The Effect of Light Emitting Diode Phototherapy on the Rate of Orthodontic Tooth Movement - A Clinical Study

by

Dr. Sean Everett Victor Chung

A thesis submitted in conformity with the requirements for the degree of Master of Science
Faculty of Dentistry
University of Toronto

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Master of Science

Faculty of Dentistry

University of Toronto

2013

Abstract

Increasing the rate of orthodontic tooth movement (OTM) can reduce risks such as periodontal disease and caries. This study investigated whether light emitting diode (LED) phototherapy could accelerate the rate of OTM. Orthodontic patients with bilaterally symmetric extraction of premolars were recruited. During space closure, LED phototherapy was applied to one side of the dental arch for a specified time and the contralateral side acted as the control. Space closure was measured immediately prior to, during and later in space closure. All 11 patients were compliant with LED application. The results revealed no significant changes in the rate of OTM with LED phototherapy over 3 months of extraction space closure. The findings were contrary to previous findings with laser phototherapy and could be related to the dosage or method of LED phototherapy delivery. Further investigations are needed to determine whether LED phototherapy application can influence the rate of OTM.
I would like to thank the following people for their contributions during my Orthodontic training. Each of you has added to my personal and professional development over the years and for this I am grateful.

Drs. Bryan Tompson, Siew-Ging Gong and Cameron Clokie, committee members who supported and encouraged the development of my research interests and the completion of this project in a timely and successful manner.

Biolux Research Ltd. for their generous donation of the LED devices which were evaluated during this study.

The Graduate Orthodontic residents, Bronsen, Christine, Heather, Kevin, Laurene, Marc and Natoosha, for your help and enthusiasm during the orthodontic component of this study. Christine, Heather and Marc, our three years have been memorable and fun-filled. I couldn’t have asked for better co-residents. We did it!

My family and friends, for your continual interest and support throughout my educational journey.
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<th>Description</th>
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<tbody>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>BMP</td>
<td>Bone morphogeic protein</td>
</tr>
<tr>
<td>CGRP</td>
<td>Calcitonin gene-related peptide</td>
</tr>
<tr>
<td>CSF</td>
<td>Colony stimulating factor</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>IR-LED</td>
<td>Infrared light emitting diode</td>
</tr>
<tr>
<td>Laser</td>
<td>Light amplification by stimulated emission of radiation</td>
</tr>
<tr>
<td>LED</td>
<td>Light emitting diode</td>
</tr>
<tr>
<td>LLLT</td>
<td>Low level laser therapy</td>
</tr>
<tr>
<td>M-CSF</td>
<td>Macrophage colony stimulating factor</td>
</tr>
<tr>
<td>MMP</td>
<td>Matrix metalloproteinases</td>
</tr>
<tr>
<td>NiTi</td>
<td>Nickel titanium</td>
</tr>
<tr>
<td>OPG</td>
<td>Osteoprotegrin</td>
</tr>
<tr>
<td>OTM</td>
<td>Orthodontic tooth movement</td>
</tr>
<tr>
<td>PDL</td>
<td>Periodontal ligament</td>
</tr>
<tr>
<td>PGE</td>
<td>Prostaglandin E</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>Tensigrity</td>
<td>Tension dependent cellular integrity</td>
</tr>
<tr>
<td>TIMP</td>
<td>Tissue inhibitor of metalloproteinases</td>
</tr>
<tr>
<td>TNFα</td>
<td>Tumour necrosing factor α</td>
</tr>
<tr>
<td>TRAP</td>
<td>Tartrate-resistant acid phosphatase</td>
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Chapter 1: INTRODUCTION

1.1 Overview

Orthodontic treatment typically lasts approximately two years. Extended treatment duration can be associated with increased risks of root resorption, periodontal disease, caries and changes or loss of patient motivation (Mizrahi, 2010; Krishnan et al., 2007; Sergl et al., 2000). Increasing the rate of orthodontic tooth movement (OTM) could reduce these risks. Additionally, the scheduling associated with multiple clinic visits to receive orthodontic treatment can become challenging for patients due to time away from school, work, extracurricular and recreational activities, etc. Improvements in treatment efficiency can help to alleviate these challenges.

Various attempts to increase the rate of OTM have been investigated (da Silva Sousa et al, 2011; Showkatbakhsh et al., 2010; Bartzela et al., 2009; Seifi et al., 2007; Youssef et al., 2008; Cruz et al., 2004; Seifi et al, 2003; Hashimoto et al., 2001; Soma et al., 2000; Kobayashi et al., 1998, Spielmann et al., 1989; Yamasaki et al., 1984). This study focused on determining if light emitting diode (LED) phototherapy could accelerate tooth movement in patients undergoing orthodontic treatment. As the effects of LED phototherapy on OTM in humans have not been previously described, this study will lay a foundation for understanding the effects of LED phototherapy on OTM rate. This study will offer opportunities to understand the cellular and molecular mechanisms that underlie OTM. Within dentistry, these findings can be applied to all branches of oral health concerned with disease management, wound healing and tissue regeneration. Furthermore, these findings will support the development of further research opportunities into the cell and molecular responses to LED phototherapy and phototherapy as a
whole while establishing a deeper understanding of connective tissue biology that will be transferable to future researchers and end-users.

This chapter of the review of the literature will be divided into 3 subsections. It will begin some of the basic principles of OTM at the cellular, molecular and clinical levels. Next, the concept of phototherapy from both lasers and LEDs will be discussed at the cellular, tissue, animal, human and OTM levels. Finally, a premise for the use of LED phototherapy in OTM will be described and the hypothesis of the study stated.

1.2 Orthodontic Tooth Movement - Biological Concepts

The phenomenon of OTM relies on bone remodelling, similar to the constant renewal of the skeleton as first described by Frost (1963). During OTM, the application of forces create compression and tension zones in the periodontal ligament (PDL) and surrounding alveolar bone to produce bone metabolic changes. Thus, these are potential targets of biological modulation of OTM.

There are two generally accepted theories to describe the series of events that result in tooth movement: The Piezoelectric Theory and the Pressure-Tension Theory (Graber et al., 2012; Proffit et al., 2007; Meikle et al., 2006; Zengo et al., 1973). It is generally accepted that a force applied to teeth causes some degree of bone bending due to the viscoelastic nature of the PDL. The Piezoelectric Theory describes that, at the macroscopic level, bone bending is associated with the creation of streaming potentials as ionic flow in the crystalline structure of the bone is produced through the bending and relaxation of the bone. In addition to these electrical currents, the Pressure-Tension Theory describes the distortion of the PDL and
supporting bone produce variations in blood supply and the release of pro-inflammatory and inflammatory cytokines in the peri-radicular tissue. The downstream result of these changes is the recruitment of multinuclear giant cells, osteoblasts, osteoclasts and fibroblasts to produce OTM (Graber et al., 2012; Proffit et al., 2007; Meikle et al., 2006; Zengo et al., 1973).

During OTM, the degree and duration of PDL and bone compression also affect the process of bone remodelling and therefore the rate of tooth movement. Undermining (indirect) resorption occurs on the compression side of a tooth when a relatively high amount of force produces a limited degree of PDL cell necrosis and an osteogenic stimulus. The result is an osteogenic response of alveolar bone remodelling from the alveolar bone side of the PDL, a process that is associated with reduced OTM rate. In comparison, frontal (direct) resorption describes the remodelling process that occurs when lighter forces (eg. 50-150g) stimulate bone resorption from the periodontal ligament side of the periodontal apparatus without cellular necrosis and therefore a relatively faster rate of OTM (Proffit et al 2007; Masella and Meister, 2006; Meikle et al., 2006).

More recently, researchers have described the mechanisms by which forces applied to a tooth affect metabolic changes at the cellular levels. Forces applied to teeth result in cell membrane distortions and changes in tension-dependent cellular integrity (Tensigrity) (Krishnan and Davidovitch, 2009). Tensigrity describes pre-existing intracellular tensile stress derived from microfilaments, microtubules and intermediate filaments that convey a physical link between the nucleus and cell-surface adhesion receptors. When forces are experienced at the PDL and bone level, they are transferred to the cell and cause cell matrix distortions that alter transmembrane proteins, integrins, focal adhesions and cell gene expression to influence intracellular protein cascade events that affect cellular metabolism, cytokine and protein production such as TNFα, IL-1 and 6, PGE₂, Substance-P, MMPs 8 and 13, BMP, TIMPs and
CGRP (Krishnan and Davidovitch, 2009; Masella and Meister, 2006; Meikle, 2006). Together, the result is the modulation of the RANK-RANKL-Osteoprotegrin (OPG) pathway such that in an area of compression, bone is resorbed and in the area of tension bone is deposited (Krishnan and Davidovitch, 2009; Masella and Meister, 2006; Meikle, 2006). The extent of bone remodelling is limited by the compartmentalization and the creation of a local vascular environment involved in the differential expression of RANK/RANKL/OPG and other cytokines around a tooth during orthodontic force application. This is referred to as the “Basic Multicellular Unit” around an orthodontically moving tooth (Eriksen, 2010; Boyce and Xing, 2008).

Despite the histological similarity to inflammation, changes in the PDL during OTM have been described as undergoing aseptic inflammation (Ren and Vissink, 2008) or a “form of normal physiological turnover combined with foci of tissue repair, particularly at the compression sites where hyalinized tissue and adjacent bone and cementum are being remodelled” (Meikle, 2006). Since phototherapy has been shown to produce inflammatory and connective tissue metabolic changes (described below), these aseptic inflammatory processes are a potential site for phototherapy mediated changes in the rate of OTM.

1.3 Orthodontic Tooth Movement: Rate and Methods to Increase the Rate

It is widely accepted that the rate of OTM varies from individual to individual. However, clinical experience combined with scientific evidence points towards an average rate of OTM of 1mm per month (Barlow and Kula, 2008). As an alternative to surgically derived regional accelerations of OTM (Wilcko et al., 2010), several studies have attempted to expedite orthodontic treatment by increasing the velocity of OTM via pharmacological and
electromagnetic modulations of the biological processes involved in bone metabolism (*described above*). There have been several publications describing a positive effect on bone metabolism and OTM with the delivery of vitamin D (Collins and Sinclair, 1988), prostaglandin E₁ and ₂ (Lee et al., 1990; Yamasaki et al., 1984), osteocalcin (Kobaysashi et al., 1998), parathyroid hormone (Soma et al., 2000; Gianelly and Schnur, 1969), long-term or high dose corticosteroids (Gonzales et al., 2009; Kalia et al., 2004; Ashcroft et al., 1992), thyroxin (Tyrovola and Spyropoulos, 2001), pulsed electromagnetic fields (Stark and Sinclair, 1987), low intensity ultrasound (Hadjiargyrou et al., 1998) and low level laser therapy (LLLT) (Genc et al., 2012; Doshi-Mehta and Bhad-Patil, 2011; da Silva Sousa et al., 2011; Bartzela et al., 2009; Youssef et al., 2008; Cruz et al., 2004; Hashimoto et al., 2001; Soma et al., 2000; Kobayashi et al., 1998; Yamasaki et al., 1984). Although successful, the major drawback to most of these treatment interventions is the necessity for systemic delivery and the ensuing systemic side effects of pharmacological agents. Alternatively, local delivery of the pharmacological agent requires repeated painful injections while delivery of phototherapy using LLLT necessitates demanding scheduling challenges with the need for repeated and frequent treatment.

1.4 Phototherapy

There is increasing application for phototherapy in areas of wound healing, tissue repair and regeneration and reductions in dental sensitivity and post-surgical and post-orthodontic adjustment pain (Dosi-Mehta and Bhad-Patil, 2012; Barolet and Boucher, 2010; de Paula Eduardo et al., 2010; Xiaoting et al., 2010; Torammano et al., 2009; Trelles and Allones, 2006; Weiss et al., 2005; Meguro et al., 2002). Phototherapeutic applications are reliant upon the biostimulatory effects of phototherapy. The term “biostimulation” was first introduced in the
1960’s to describe the “photochemical interactions” of low intensity lasers with tissue (Niemz 2007; Desmet et al., 2006; Sommer et al., 2001) and has since also been referred to as photostimulation, photomodulation and photobiostimulation.

Phototherapy is hypothesized to produce biostimulatory effects from increased blood circulation (Cruz et al., 2004) and pro-inflammatory mediators such as IL-1β (Saito and Shimizu, 1997) and PGE₁ (Yamasaki et al., 1984) increased ATP availability and cell metabolism via the removal of electron deficits by the appearance of singlet oxygen or by direct stimulation of the electron carriers (cytochrome c oxidase) in the electron transport chain (Bashardoust Tajali et al., 2010; Conlan et al., 2006; Desmet et al., 2006; Karu et al., 2005; Eells et al., 2004) and/or increased Na⁺/K⁺ pump activity and intracellular Ca²⁺ causing augmentation of protein synthesis as well as DNA and RNA replication to accelerate cell metabolism (Bashardoust Tajali et al., 2010; Coombe et al., 2001).

It is hypothesized that the biostimulatory effect of phototherapy is governed by the Ardnt-Schultz law (Figure 1.1), where a low-moderate level of energy is required to achieve cell activation but excess energy results in cell retardation (Kim et al., 2009; Sommer et al., 2001).

![Figure 1.1](image_url) The Ardnt-Schultz effect describes the observation of a stimulatory effect in response to a low-moderate dose of an intervention whereas an inhibitory response is seen when higher doses of an intervention/drug are used.
Furthermore, “due to the cooperative behavior of photostimulated cells, it is important to irradiate the application field simultaneously to avoid adverse effects with respect to the intended aims...creating a homogenously distributed mean energy density with the necessary local light intensity, as required for activation” (Sommer et al., 2001). In other words, to observe biostimulation, phototherapy should be delivered to the entire field of tissue uniformly. Thus, two conceptual methods of delivering phototherapy include lasers (eg. LLLT) and LEDs (Vladimirov et al., 2004; Karu, 2003; Sommer et al., 2001).

**Figure 1.2** The comparison of sunlight, LED and lasers. Sunlight is composed of light of various wavelengths, and amplitudes. LED light is composed of light that has a narrow wavelength and amplitude, with low spatial coherence. Laser light displays spatial and temporal coherence of light with a narrow wavelengths and amplitude.
In general, when electromagnetic radiation (i.e. laser or LED) is applied to tissues, it is reflected, transmitted, scattered and/or absorbed. This can result in different effects, e.g., photochemical (photonomically induced chemical reactions), photothermal (alterations to chemical bonds resulting in heat, ablation and/or coagulation) and photomechanical or photoionizing (cell damage resulting from destruction of cell membranes, proteins and/or DNA) effects (Graber et al., 2012; Norton et al., 2008).

The term “laser” (Light Amplification by Stimulated Emission of Radiation) was first proposed by Gordon Gould in 1957 and describes a form of electromagnetic radiation with a very narrow wavelength and focus. In comparison to sunlight, laser light is coherent in nature, with a fixed relationship between the electric field values at different locations (spatial coherence) or at different times (temporal coherence). It is generated in a resonator and emitted continuously or in a pulsed manner, such that they are propagated over long lengths without divergence (Paschotta, 2008).

Lasers are classified according to their ability to produce tissue damage. The classification of a laser is dependent upon the characteristics of power, wavelength, exposure and cross-sectional area of the laser beam. In accordance with the International Electrotechnical Commission, the safety of lasers is expressed in terms of maximum permissible exposure, describing the highest power that tissues can be exposed to without damage. The safety ratings range from 1 which is safe under all conditions to the maximum 4 which is always hazardous to view and has devastating damage to the eye and skin and with an ability to ignite material. Additionally, within the first and second safety ratings is a sub-category denoted as “M”, referring to the power not exceeding a certain limit as measured through a 7mm aperture at a distance of 10cm from the source (Graber et al., 2012).
Typically, lasers used in phototherapy are in the 1M category (denoting a low intensity and hence the term LLLT). Although lasers can be set to emit different wavelengths, an infrared (IR) wavelength (approximately 600-1000nm) in the range of approximately 730-850nm is viewed as the most appropriate to promote biostimulation as well as increases in OTM (Yoshida et al., 2009; Kocoklu-Altan et al., 2009; Desmet et al., 2006; Karu et al, 2005; Eells et al., 2004; Schieke et al., 2003; Stolik et al., 2000).

1.5 Light Emitting Diodes - An Alternative to Low Level Laser Therapy

In contrast to lasers (Figure 1.2 and Table 1.1), LED light is generated via electroluminescence (light emission triggered by electric influences, eg. electron beam) to produce a light with low spatial coherence; being emitted in all directions with low focusability and a wider wavelength range. LEDs benefit from low energy consumption and low heat emission. As with lasers, the wavelength of the emitted light is dependent on the material that is used to generate the light emission, with a combination of Gallium-Arsenide-Aluminum (GaAsAl) producing IR-LED in the 680-860nm range. These characteristics of LEDs help explain why their typical uses include: LED displays, ambient lighting, signal lights, cellular phone displays, TV screens and street lights. (Paschotta, 2008)

The form of the light energy (i.e., LLLT or LED) does not appear to be a prerequisite for biostimulatory effects given that “under physiological conditions, the absorption of low-intensity light by biological systems is of purely non-coherent (i.e., photobiological) nature” (Karu, 2003). Since lasers are coherent in nature, targeting a region of tissue would necessitate the combination of high powered lasers with optical lenses. However, this adaptation can be very expensive. Lasers also have limitations in wavelength capabilities and beam width, the potential for significant heat production which can burn tissue, the potential for eye damage due
to the narrow focus of the beam and a greater cost when compared to LED devices (Casalechi et al., 2009, Eells et al., 2004). Furthermore, lasers require the clinician to deliver the exposure to the patient on a regular basis, rather than the patient themselves. Given the potentially limiting characteristics of lasers in terms of regional tissue application, LEDs stand to be a promising alternative for biostimulation (Vladimirov et al., 2004; Sommer et al., 2001) with the potential to be more effective and practical as a medium to uniformly deliver energy to an entire field of tissue and to influencing OTM.

<table>
<thead>
<tr>
<th>Table 1.1</th>
<th>LASER</th>
<th>LED</th>
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<tr>
<td>Cost</td>
<td>▲</td>
<td>▼</td>
</tr>
<tr>
<td>Safety</td>
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<td>Heat</td>
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<tr>
<td>Focus</td>
<td>Narrow</td>
<td>Wide</td>
</tr>
<tr>
<td># Clinic visits</td>
<td>▲</td>
<td>=</td>
</tr>
<tr>
<td>Beam</td>
<td>Coherent</td>
<td>Incoherent</td>
</tr>
<tr>
<td>Energy use</td>
<td>▲</td>
<td>▼</td>
</tr>
<tr>
<td>Device size</td>
<td>Large</td>
<td>Small</td>
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</table>

Table 1.1 A Comparison of the Characteristics of Lasers and Light Emitting Diodes

Regardless of the mechanism behind biostimulation, the downstream effects of phototherapy have been observed as increased cellular proliferation, collagen and procollagen synthesis, the release of growth factors from cells, enhanced fibroblast and osteoblast activity, collagen and bone formation, calcium and phosphate incorporation, nerve stabilization, ATP production and reductions in pH, MMP-8, collagenase activity, IL-1, TNF and interferon when lasers are used in treatment (Abi-Ramia et al., 2010; Youssef et al., 2008; Desmet et al., 2006;
Sommer et al., 2001). These findings have prompted the use of lasers alone or in combination with traditional therapeutic approaches in periodontics, oral surgery, endodontics, and restorative procedures, and more recently, orthodontics (Walsh, 2003).

Clinical benefits that have been described with the use of LLLT include the reduction of post-surgical and post-orthodontic adjustment pain and gingival health, improvements in post-surgical healing times, antimicrobial effects and the ability to reduce dentinal sensitivity (Bicakci et al., 2012; Doshi-Meha and Bhad-Patil, 2012; Esper et al., 2011; Bashardoust Tajali et al., 2010; de Paula Eduardo et al., 2010; Xiaoting et al., 2010; Torammano et al., 2009; Fujiyama et al., 2008; Youssef et al., 2008; Turhani et al., 2006; Meguro et al., 2002; Harazaki et al., 1998; Luger et al., 1998; Saito and Shimizu, 1997; Lim et al., 1995). However, despite the recent recognition of phototherapy to produce biostimulatory effects, more clinical studies to discern the mechanism of action are needed (de Paula Eduardo et al., 2010).

1.6 The Role of Low Level Laser Therapy in Orthodontic Tooth Movement

In an attempt to elucidate the mechanisms behind biostimulation, in vitro experiments have shown that LLLT increases the number of osteoclasts (Aihara et al., 2006), fibroblasts (Vinck et al., 2003) and the rate of proliferation and DNA synthesis of clonal osteoblastic cells (Yamada, 1991) with such changes associated with increased pulp vascularity (Abi-Ramia et al., 2006), protease activity (Yamaguchi et al., 2010) and connective tissue (Kim et al., 2010) and bone turnover (Habib et al., 2010; Yoshida et al., 2009). Furthermore, LLLT has been found to result in increases in RANK expression (Fujita et al., 2008; Aihara et al., 2006), RANKL (Fujita et al., 2008), TRAP (tartrate-resistant acid phosphatase - indicative of osteoclastic activity) (Kawasaki et al., 2000), M-CSF (macrophage colony stimulating factor) and csf-1 (colony
stimulating factor-1) (Yamaguchi et al., 2007); implicating major involvement in signaling pathways of bone metabolism and OTM. Evidence of such implications have been shown in animal experiments where LLLT enhanced bone fracture healing (Bashardoust et al., 2010; Hadjiargyrou et al., 1998; Luger et al., 1998) and the rate of OTM (Habib et al., 2012; Goulart et al., 2006). These and other studies of similar nature have underwritten the potential for LLLT to influence OTM in humans.

Although the effects of LLLT on OTM in humans are limited and mixed results, several studies (Table 1.2) have shown the effect of LLLT on OTM during canine retraction using a split-mouth design. There have been 2 reports citing no significant effect of LLLT on OTM. The lack of effect was cited as a result an incorrect phototherapy dose leading to reduced levels of arachadonic acid and PGE₂, with subsequent reductions in osteoclastic activity and enhancement of osteoblastic activity. Despite no notable benefits on OTM, these studies demonstrated that there were no iatrogenic effects resulting from LLLT exposure (Kocoglu-Altan et al., 2009 Limpanichkul et al., 2006).

Conversely, several studies have demonstrated positive effects of LLLT on OTM (Genc et al., 2012; Doshi-Mehta and Bhad-Patil, 2011; da Silva Sousa et al., 2009; Youssef et al., 2008; Cruz et al., 2004). The majority of these studies concluded that the application of LLLT increased the amount of OTM by approximately 15-95% during canine retraction in a split-mouth design over 1-4 months (Table 1.2). They also described no differences in root resorption or crestal bone loss associated with LLLT during OTM (Doshi-Mehta and Bhad-Patil, 2011; da Silva Sousa et al., 2009; Youssef et al., 2008; Cruz et al., 2004). Together, these studies illustrated that although the dose dependent effect of LLLT has not yet been determined, LLLT can affect bone metabolism and OTM at the cellular, animal and human levels without any harmful effects.
<table>
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<th>Author, year</th>
<th>Mos</th>
<th>N</th>
<th>Age (yrs)</th>
<th>Rx days</th>
<th>Laser λ (nm)</th>
<th>Power (W)</th>
<th>Energy Density (J/cm²)</th>
<th>Energy Dose/ apt. (J)</th>
<th>Time applied / apt. (sec)</th>
<th>Wire size</th>
<th>Force level (g)</th>
<th>Laser (mm)</th>
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<td>18 SS</td>
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<td>Cruz et al., 2004</td>
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<td>2</td>
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<td>1.98+/-.046</td>
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**TABLE 1.2** The effects of LLLT on OTM during canine retraction with a split mouth design. (*denotes p<0.05, when comparing lasers to controls)*
1.7 Light Emitting Diodes – Cell, Molecular, Tissue and Metabolic Effects with a Potential Role in Orthodontic Tooth Movement

The reports on the effects of LED phototherapy on tissue and OTM are more limited than that of LLLT (lasers). At the cellular level, it has been demonstrated that peak absorption measurements of cellular monolayers occur in the range of 730-850nm (Karu et al., 2005). Furthermore, LED phototherapy has been shown to increase mesenchymal stem cell and fibroblast proliferation (Li et al., 2010; Vinck et al., 2003), DNA replication, cell adhesion (Karu et al., 2005), cell growth, proliferation rates and mitochondrial activity, while rescuing mitochondrial dysfunction (Holder et al., 2012). These findings are consistent with animal studies showing enhanced wound healing and tissue regeneration (Rosa et al., 2013; Tada et al., 2009; Casalechi et al., 2009; Al-Watban et al., 2006; Whelan et al., 2003), decreased inflammation (Fonseca et al., 2013), increased mini-implant stability (Uysal et al., 2010) and increased periodontal tissue vascularity and repair during OTM (Fonseca et al., 2013).

At the clinical level, the safety and benefits of LED phototherapy have been demonstrated in other health fields than dentistry as reduced healing times and post-surgical post erythema, increased medicament absorption (Barolet and Boucher, 2010), accelerated re-epithelialization and decreased symptoms (burning, peeling, redness, swelling, peeling) (Trelles and Allones, 2006; Weiss et al., 2005). Although very limited, the dental benefits have been reported as positive effects on socket preservation (Brawn et al., 2007) using LED phototherapy 10 minutes per day for 21 days (600-650nm, 12J/cm², 3.6cm²) and reduced pain associated with OTM when applied for 70 seconds (640nm, 4J/cm², 0.1W) at a given orthodontic appointment (Esper et al., 2011).
Despite the similarities in the effects of LED phototherapy to LLLT, there have been no publications on the effects of LED phototherapy on OTM in humans to date. Given the safety of LEDs as compared to lasers (Casalechi et al., 2009, Eells et al., 2004) and the fundamental similarities at the biological level, this study investigates the role of LED phototherapy on OTM with the intention of establishing a foundation for IR-LED phototherapy mediated increases in OTM rates. This study will also offer opportunities to understand the cellular and molecular mechanisms that underlie OTM and possibly tissue repair/regeneration and in more general terms, connective tissue metabolism.

1.8 HYPOTHESIS

The overall hypothesis of this study is that IR-LED phototherapy can alter the rate of OTM over the first 3 months of active extraction space closure. To address this hypothesis, patients undergoing bilaterally symmetrical extraction space closure will be exposed to IR-LED phototherapy in a split mouth manner.
Chapter 2: MATERIALS AND METHODS

2.1 Study design and approvals

This study was reviewed and approved for scientific validity and methodology by the Dental Research Institute of the University of Toronto, Faculty of Dentistry. All protocols were approved by the University of Toronto, Research Ethics Board (approvals shown in Appendix A). This study has been registered at www.clinicaltrials.gov.

2.2 Patient selection

Patients undergoing treatment at the University of Toronto, Faculty of Dentistry, Graduate Orthodontics clinic were recruited for the study. All participating patients were previously treatment planned by supervising certified specialists in orthodontics and required bilaterally symmetric extraction of first or second premolars. The following inclusion and exclusion criteria were applied:

**Inclusion criteria:**

- Age ≥ 11 years old
- Fixed edgewise appliance therapy of all permanent teeth
- Treatment planned for bilaterally symmetrical extraction of first or second premolar teeth
- Presence of adequate residual extraction space size (after the correction of crowding) large enough to require more than 1 orthodontic appointment interval for complete space closure
• Space closure of extraction site to be performed on stainless steel wire of dimensions ≥ 0.018” OR ≥ 0.016’ x 0.022”

**Exclusion criteria:**

• Presence of systemic illnesses
• Current exposure to medicines
• Pregnancy
• Previous orthodontic therapy
• Smokers

Potential participants (and parents and guardians) were verbally informed of the study rationale and design. In addition, they were provided with written documents detailing information that included the following: privacy and security policies for use of their personal information in the study, a description of the LED device, a user manual for the LED device, documentation illustrating the safety of the LED device and an overview of the study validity, rationale and protocol (see Appendix A). Patients were then given the opportunity to review the documents at their leisure and had all questions answered prior to consenting to participate in the study.

Following informed consent, all potentially participating patients were monitored until extraction space closure was to be actively undertaken. If the extraction spaces were viewed as being fairly symmetric and of adequate size (see inclusion criteria above) they were included in the study. These patient recruitment parameters yielded 37 potential study participants of which 11 patients were finally included in the study.
2.3 Orthodontic Extraction space closure and extraction space size assessment

**Preparation for space closure**

Orthodontic treatment was delivered by Graduate Orthodontic residents who were previously informed of the design of the experiment. At times, orthodontic treatment proceeded routinely and was not altered to accommodate this clinical study. All patients underwent routine orthodontic therapy in preparation for extraction space closure. This preparation included the aligning and levelling of teeth (see Figure 2.1) such that space closure could be performed on stainless steel working wires of dimensions $\geq 0.018''$ OR $\geq 0.016' \times 0.022''$. Space closure was conducted in a routine manner after working wires were passively in place for $\geq$ than 1 month.

![Figure 2.1 Preparation for extraction space closure.](image)

Prior to space closure, bilaterally symmetrical premolars were extracted. Subsequently, the teeth in the dental arch were aligned and leveled. The left image illustrates a starting malocclusion while the right image shows a typical dental arch ready to begin active space closure and the start of data collection.
**Extraction space closure mechanics**

Extraction space closure was conducted with sliding mechanics delivered by constant force nickel-titanium coil springs (DENTSPLY GAC International) with a force level of 150g (Figure 2.2). In all cases a reinforced anchorage system was employed such that the tooth anterior to the extraction space was retracted towards the posterior dental segment.

![Extraction space closure](image)

**Figure 2.2 Extraction space closure.** Constant force NiTi coil springs (150g) were used to conduct active extraction space closure.

**Extraction space size assessment**

Measurements of the extraction spaces were taken at three time points:

- Time point 0 (T0) = Day of initiation of space closure
- Time point 1 (T1) = 4-7 weeks after the initiation of space closure (T0)
- Time point 2 (T2) = 3-7 weeks after T1

At each time point dental impression were taken using stock mental dental impression trays and an extended-time, dimensionally stable, chromatic indicating and irreversible hydrocolloid impression material (Kromopan). All dental models were poured in Vel-Mix white Type IV die stone (Kerr Dental Laboratory Products) within 24 hours by the same individual.
Extraction space measurements in duplicate were undertaken independently by 2 observers who were blinded to which side of the arch had received LED phototherapy. Therefore, a total of 4 measurements for each space were recorded. The extraction space size was defined as the interproximal distance, as measured by a horizontal line parallel to the archwire/archwire slot, between the mesial-most and distal-most surfaces of teeth distal and mesial, respectively, to the extraction space in both vertical and horizontal dimensions (Figure 2.3). That is, the millimetric measurements were taken with a high precision digital caliper (Tresna, model EC-10, ID 110-201, resolution 0.005mm, accuracy 0.025mm) which measured the two closest points between the crowns of the teeth ahead of and behind the extraction space (Figure 2.3).

The rate of tooth movement for each patient was calculated by dividing the millimetric change in size of the extraction space by the total days for each time period.

**Figure 2.3 Extraction space measurements.** All measurements were made without knowing which side of the dental arch had received LED phototherapy. A digital caliper was used to measure the extraction space. It was determined as the shortest distance between the mesial- and distal-most points (blue arrows and red lines) of teeth distal and mesial to the extraction space, respectively, when viewed from the buccal and occlusal perspectives. Measurements were taken with the caliper oriented parallel and perpendicular to the arch wire (yellow line).
2.4 Light Emitting Diode Device and Use

The LED device used was provided by BIOLUX RESEARCH LTD (device description in Appendix A4). Device characteristics:

- is a class 1-M laser (and is therefore relatively safe)
- provided extra-orally derived, transdermal infrared light to a given target area
- had a wall mounted power source
- had a controller that indicated the time remaining for each treatment, the number of treatments completed and controlled the activation of specific LED arrays
- featured a face detection mechanism to permit monitoring and reinforcement of compliance

**LED device specifications:**

- 220mA/array, 850nm, 150mW/cm^2
- within alveolus= 1-10mW/cm^2 (pilot readings: 0.92-6.92J/cm^2)
- will not exceed 41 degrees

**LED prescription and other patient instructions**

The LED light was delivered using a randomly allocated split mouth design. In each case, the facemask (Figure 2.4 D) was adjusted for each patient to ensure that the LED array was parallel to the occlusal plane of each patient. Furthermore, the LED array was positioned to target the root of the tooth being retracted as well as the extraction site into which the tooth would be moved. (Figure 2.4 C)
Figure 2.4 The BIOLUX LED device. A) The hard plastic case with sponge insulation in which the LED device was provided to each patient to lessen against impact damage. B) Each device was composed of a face mask with LED arrays, a power supply and a hand-held controller unit. C) Each face mask unit was positioned to ensure a firm and reproducible position on the face with the LED arrays parallel to the occlusal plane of the patient. The LED array was positioned and programmed to target the root of the tooth undergoing retraction as well as the extraction space into which the tooth was being moved on only one side of the face. D) Although visibly noticeable in C, the LED illumination is not visible to the naked eye.
Patients were instructed on how to safely place, use and remove the device and how to store and transport the device (Figure 2.4 A-D). The application of LED device was given to each patient in accordance with the manufacturer’s recommended LED device use of 21 minutes per day (i.e., one phototherapy cycle). This protocol was based on prior studies on the effect of low level laser therapy and on pilot studies by the manufacturer assessing the intra-alveolar light received from the current LED device. Therefore, patients were instructed to complete one LED cycle per day until their next orthodontic appointment (i.e. T1 or T2).

Compliance was logged by the device’s controller. In addition, a manual record of LED use was also kept by each patient, using a paper calendar to document the days on which they completed an LED phototherapy cycle. The compliance rate for each patient in a given time period was calculated by dividing the number of days of LED use by the total prescribed days of LED phototherapy.

### 2.5 Data and Statistical Analysis

For each patient the following data was collected:

- Age
- Sex
- Wire size during the extraction space closure phase
- Extraction space size at T0, T1, T2
- The side of the dental arch that received LED phototherapy
- The number of days that the LED was used (device data log and paper calendar)
- The number or days for each time period (T0→T1) and (T1→T2)
Statistical Analysis

All statistical testing including the determination of normality and equal variance was performed using commercial software SAS 9.2. A 5% significance level and 95% confidence intervals were used for all tests. (Statistical test results can be found in Appendix B)

To test for inter-rater and intra-rater reliability, intra-class correlation coefficients were performed on the data sets. Given that an excellent level of reliability was found, the first set of data from the first observer was used for all subsequent statistical analysis.

Each dental arch was treated as independent of each other and as such all statistical analysis was conducted in such terms. Descriptive statistics on age, extraction space size and LED exposure and compliance were calculated (Table 3.1). To account for the possibility that each arch can have its own starting extraction space size (y-intercept in Figures 3.4 and 3.5) and rate of space closure (slope in figures 3.4 and 3.5), a random effects model was used.

To compare the change in the size of the extraction space over time, the data was analyzed using repeated measures linear models to assess the effect of LED exposure and time, adjusted for cumulative LED, wire size, sex and age. Quadratic models were also explored to determine if it was a better description of the data. Furthermore, to see if there were any appreciable differences associated with the cumulative LED phototherapy exposure for each patient, averages at 4 arbitrary time points (20, 45, 60 and 80 days) were extrapolated and the differences in the rate of space closure where compared.
Chapter 3: RESULTS

3.1 Patient Sample

A total of 220 patients were screened at the pre-experimental orthodontic phase that included routine orthodontic treatment with fixed edgewise appliance. Of these patients, only 37 presented with treatment plans requiring bilaterally symmetrical extractions of either first or second premolars. From this group, only 11 patients satisfied the inclusion and exclusion criteria of the study. These 11 patients had an average age of 16.07 (+/- 1.48) years and with a range of 13.96 – 17.75 years (Table 3.1). In 6 patients, both dental arches were included in the study whereas only one arch was included for the remaining 5 patients. As each dental arch was independent of each other, measurements were taken and analyzed on a total of 17 dental arches (N=17; 11 males and 6 females), with 9 maxillary and 8 mandibular arches. First premolars were extracted followed by canine retraction in 12 cases, whereas in the remaining 5 cases, second premolars were extracted followed by retraction of the first premolars. The process of closing the residual extraction space occurred on stainless steel wires with rectangular dimensions greater than or equal to 0.016”x0.022” in 13 arches or with round dimensions greater than or equal to 0.018” in 4 arches.

3.2 Experimental Time Periods

Space closure of the extraction sites was measured at 3 time points of orthodontic care. All 17 dental arches were included in the measurements of the first time period that spanned the start of space closure (T0) and the first orthodontic adjustment appointment into space closure (T1). On average, the duration of this first period was 5.48 weeks with a range of 4-7 weeks
However, in 4 arches the remaining extraction space was anticipated to completely close prior to the next orthodontic adjustment appointment (T2) and was therefore excluded from subsequent measurements. Therefore, 13 dental arches were included for the time period from T1 to T2. The duration of time between the first (T1) and second (T2) orthodontic adjustment appointment into space closure was 5.49 weeks with a range of 3-7 weeks (Table 3.1).

### 3.3 Compliance with the use of the LED Appliance

Consistent with a split-mouth design, the LED was applied to only one side of the dental arch during space closure. In 8 cases it was applied to the right side and in 7 cases it was applied to the left side. Values generated by the LED device corresponded (100%) with manual records of the patients. The degree of compliance was 78.04% of the prescribed time with a range of 25.8-92.9% from T0 to T1 (LED compliance reported as days, Table 3.1). This compliance rate equated to an average of 30.29 (S.E.M. = 2.13) days of LED use, with a range of 9-40 days. LED use during the second experimental period (T1-T2) was similar, with a compliance of 82.35% (range 61.9-100%) resulting in an average of 32.54 (S.E.M. = 1.94) days of LED application with a range of 19-48 days (Figure 3.1).

### 3.4 Measurement and Analysis of Space Closure

Space closure was assessed at 3 time points: prior to space closure (T0), the 1st appointment into space closure (T1) and a subsequent (2nd) appointment into space closure (T2). The reliability of the recorded data from each of the two raters revealed that the inter-rater and
intra-rater reliability was >0.98. Based on this high degree of reliability, the first data set was used for all further statistical analysis.

For both groups the average extraction space size at the first measured time point (T0) was similar, with the LED group at 5.24mm compared to the control group at 5.08mm (Figure 3.2). In general, it was noted that for both groups the amount of space was smaller at each subsequent orthodontic visit (Figure 3.2), indicating that the extraction space was closing as expected in both control and LED groups. However, between the groups, no statistical difference was found between the extraction space sizes at T0 (LED=5.24mm, control=5.08mm), T1 (LED=3.64mm, control=3.3mm) or T2 (LED=2.75mm, control=2.95mm) (Figure 3.2, p=0.5066).

3.5 The Change in Extraction Space Size Over Time with Orthodontic Tooth Movement

In order to compare the rate of OTM (mm/d), the changes in the extraction space size over time were compared at each time point (Figure 3.3). A repeated measures comparison of the average amount of tooth movement from the start of the experiment (T0) to T1 and from T1 to T2 showed that both groups exhibited similar average rates of tooth movement throughout the study. There was no statistical difference in the average OTM rates for both time points with a rate of tooth movement of 0.04mm/d for both groups at T1 and 0.04mm/d and 0.05mm/d for the control and LED groups, respectively at T2 (Figure 3.3).

To account for the fact that the recall interval (time between T0 to T1 and T1 to T2) was different for each patient, a linear modeled repeated measures analysis comparing the individual changes in extraction space size over time with OTM of the LED-treated and control sides of each patient was conducted (Figure 3.4). In all cases except one, there was a reduction in
extraction space size from T0 to T1 and T1-T2 (Figure 3.4). In the case of the one exception in the LED group, there was a lack of tooth movement from T0 to T1 followed by a subsequent decrease in extraction space size during the second recall period. The exclusion of this data set did not affect the statistical significance of the comparison of controls versus LED-treated OTM rates.

The resulting rates of OTM for the control and LED-treated (thick, hatched red and solid blue lines, respectively; Figure 3.4) groups were described using the following line equations:

→ **LED-treated Extraction space** (in mm) = 5.227 - 0.042*days.

→ **Control Extraction space** (in mm) = 5.004 - 0.039*days.

These equations indicate that the average starting extraction space size of both groups was similar, with 5.227mm for the LED-treated side compared with 5.004mm for the control side. Also, both groups were found to have no statistically significant difference in average OTM rates with 0.042mm/d and 0.039mm/d for the LED-treated side and control sides, respectively (p=0.5066). In other words, accounting for the variation in orthodontic appointment interval length of each patient corresponded with the finding of no difference in the rate of OTM (slope of the line in Figure 3.4) between the LED treated and control sides.

Further statistical analysis was conducted to test if there were any changes in the size of the extraction space over time between the two groups which could be better described with a quadratic modeled repeated measures analysis. In a similar manner to the linear model, this analysis compared the individual change in extraction space over time of the LED-treated and control sides of each patient and revealed no significant differences (p=0.4362, Figure 3.5).
3.6 Other Factors

To address the possibility that the cumulative LED treatment could influence the rate of OTM, a least square means analysis at arbitrary time points (Days 0, 20, 45, 60 and 80) was conducted (Figure 3.6). The average extraction space size at each extrapolated time point was similar and the extraction space sizes were noted to display similar reductions in size at each of the arbitrary time point. In addition, the rate of OTM for the LED-treated and control groups was not found to be statistically different at any of the time points (Day 20, p=0.2445; Day 45, p=0.1758; Day 60, p=0.1717; Day 80, p=0.1741).

Other factors that were considered as possible influences on the rate of OTM were sex, age and orthodontic wire dimension. Repeated measures analysis using these did not demonstrate any significant influence or interactions of sex (p=0.0752), wire size (p=0.7427) or age (p=0.4117) on the rate of OTM in the two groups.

3.7 Summary of Findings

The results indicate that the patients involved in this study were demographically similar in terms of age and that distribution of the side of LED application (left or right side) was balanced. The data indicates that the starting size of the extraction site was similar in the control and LED-treated sides. As well, there was no statistical difference in the change of extraction space size over time between both groups overall or at the first (T1) or second (T2) recall periods. This finding was not altered by analyses that accounted for the effects of age, sex, wire size, cumulative LED received or possible temporal variations in OTM.
Table 3.1 Study sample descriptive statistics.

<table>
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<th>Description</th>
<th>Value</th>
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<td>Age</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Tooth retracted</td>
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<tr>
<td>Dental arch</td>
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<td>T0-T1 (weeks)</td>
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<tr>
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<td>5.49 (range 3-7), N=13</td>
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<tr>
<td>LED compliance (%)**</td>
<td>82.35 (range 61.9-100)</td>
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<tr>
<td>Total T1-T2 LED (days)*</td>
<td>32.54, SEM 1.94, range (18-49)</td>
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</table>

* patients were prescribed 1 LED cycle/day. The LED use was therefore reported as days of use.
** % compliance is in reference to the prescribed use of 1 LED cycle/day
SS= stainless steel
Figure 3.1 Total LED application

- **T1 (N=17)**
- **T2 (N=13)**

78.04% LED compliance
82.35% LED compliance

Days of LED use

Time Point

Figure 3.2 The Change in Extraction Space Size

- **Extraction space size (mm)**

- **T0 (N=17)**
- **T1 (N=17)**
- **T2 (N=13)**

LED
Control

Figure 3.3 The Average Rate of Extraction Space Closure

- **Rate of Tooth Movement (mm/d)**

- **T1 (N=17)**
- **T2 (N=13)**

LED
Control
FIGURE 3.4 The Average Change in extraction space size: A Linear Model Repeated Measure Analysis

FIGURE 3.5 The Average Change in extraction space size: A Quadratic Model Repeated Measure Analysis
Figure 3.6 The Change in Average Estimated Extraction Space

LED

Control

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<td>Day 20</td>
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<td>0.1717</td>
</tr>
<tr>
<td>Day 80</td>
<td>0.1741</td>
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</tbody>
</table>
This study investigated whether extra- orally derived, transdermal IR-LED phototherapy applied during extraction space closure was able to increase the rate of OTM. It showed that there was no statistical difference in the rate of OTM over a 3 month period of bilaterally symmetrical extraction space closure. A discussion of the design employed in the study and the possible reasons for the finding of a lack of effect of IR-LED on OTM and future directions will be conducted in the following subsections.

4.1 The Evaluation of Orthodontic Tooth Movement: Extraction Space Closure versus Changes in Overall Occlusion.

In evaluating the rate of tooth movement, studies can be categorized as quantitative if they measure the rate of tooth movement directly or qualitative if they report on treatment progression via improvements in the degree of malocclusion. This study focused on a quantitative measure of the rate of movement of specific teeth.

In contrast to the chosen mode of evaluating tooth movement, indices of malocclusion are sometimes used to categorize patients and assess treatment progress. However, indices of malocclusion often involve several variables that contribute in varying degrees to the malocclusion index rating. For example, some indices such as the IOTN (Index of Orthodontic Treatment Need) emphasize factors such as esthetics (Borzabadi-Farahani et al., 2012; Lima et al., 2010; Manzanera et al., 2010). Although important in a successful treatment outcome, these
factors are difficult to quantify and therefore are a less ideal way of assessing OTM. Other indices such as Little’s Irregularity Index are based on the average position of the anterior teeth in comparison to the ideal anterior teeth position (Macauley et al., 2012). Furthermore, the assessment of tooth position is done only in the 1st order dimension (i.e., without consideration of angulation or inclination). Similar to the IOTN, this index does not consider the rate of movement of single teeth and therefore may either over or underestimate OTM based on the starting tooth position.

In an attempt to account for inter-patient variations in malocclusion (as described above), large sample sizes are often relied upon to reduce confounding variables. However, in the case of a split-mouth design with single tooth extraction space closure using similar anchorage management, the measurement of OTM can be accurately ascertained without the variability of different starting malocclusions or variations in orthodontic appliance design from one patient to another. In the study, patients had different amounts of residual extraction space prior to space closure on one side of the dental arch verses the other. However, the focus of the study was on the rate of tooth movement (mm/d) rather than the raw amount (mm) of tooth movement using a split-mouth approach to remove inter-patient and intra-patient variation associated with differences in starting extraction space sizes, malocclusion types and the variation in inter-appointment interval (T0-T1 or T1-T2). Furthermore, to prevent the underestimation of the calculated rate of OTM, application of the exclusion criteria removed patients whose residual extraction space would not ensure space closure was not complete prior to the next orthodontic appointment. The evaluation of OTM during the single tooth extraction space closure included both canine and 1st premolar tooth retraction and was evaluated in comparison to the matching contra-lateral tooth in the respective dental arch. In this scenario (a clinical setting) the periodontal ligament and root surface areas of the comparison teeth are as
similar as a possible. In effect this ensured that the conversion of a force applied to the tooth and the resulting OTM was expected to be the same. Therefore, the application of the IR-LED phototherapy to one side of the dental arch was the only variable.

4.2 Study Design: Patient Sample and the Split-Mouth Approach

One of the challenges inherent in most clinical studies, including this study, is the recruitment of an adequate number of patients. Careful and strict application of inclusion and exclusion criteria to reduce potentially confounding variables decreased the total number of study participants. The 11 enrolled patients in this study yielded a sample size of 17 dental arches, which were treated as independent of each other in terms of the orthodontic mechanics and the presence or absence of the study intervention (IR-LED phototherapy). This sample size was within the range suggested by pre-study sample size calculations (Appendix B8) and was comparable to those that have reported on the effect of LLLT on the rate of OTM during canine retraction (Table 1.2). Four prior studies reported on 11-14 dental arches and 2 studies reported on 30 dental arches (Doshi-Mehta and Bhad-Patil, 2011; da Silva Sousa et al., 2009; Kocoglu-Altan et al., 2009; Youssef et al., 2008; Limpanichkul et al., 2006; Cruz et al., 2004). Although post-study power analyses indicated that a sample of 100 arches would ideally be needed to detect a 0.001mm per day statistical difference between groups, a more clinically relevant threshold of greater than 1mm difference between groups would necessitate less than 24 arches (Appendix B9). This study’s sample of 17 arches displayed an average age and inter-orthodontic appointment length which is representative of a typical orthodontic patient. Despite a sample size of 17 dental arches, the small range in age and inter-appointment length reduced the data
variability that a larger sample size would be intended to overcome and was within the sample size range needed for detection of a clinically relevant difference between groups.

This study relied on the benefits of the split-mouth design that permits intra-patient comparison. As opposed to inter-patient comparisons, intra-patient comparisons require much smaller sample sizes since each individual acts as his/her own control. Therefore, differences in rates of OTM between patients due to different biological conditions (e.g., differences in bone density and bone metabolism) or orthodontic appliances and biomechanics are reduced, if not eliminated. In essence, since all parameters are the same on both side of the mouth and the intervention is delivered to only half of the dental arch, this permits the evaluation of the clinical effects of the IR-LED phototherapy. There are 2 major challenges to the validity of the split-mouth design: A) the possibility that there might be a systemic effect from the LED phototherapy; and B) the possibility of photoleakage to the contralateral side of the dental arch.

A) The split-mouth design and the possibility of a systemic effect of LED phototherapy

It is expected that the greatest effects of the LED would to be at the site of LED administration. This assumption is based on the concept of the Basic Multicellular Unit of bone remodelling, where there is compartmentalization and the creation of a local vascular environment for bone remodelling (Eriksen, 2010). The basic mechanisms of bone remodelling between a targeted situation (e.g. application of an orthodontic force) versus resting state also differ. The regulation of non-targeted bone remodelling occurs through the activities of hormones like parathyroid hormone, thyroxine, growth hormone and estrogen whereas the mechanisms of localized bone remodelling are thought to involve osteocytes and RANKL (Eriksen, 2010; Boyce and Xing, 2008). In contrast, in a targeted situation osteocytes mechano-
detect force application and are involved in the differential expression of RANK/RANKL/OPG and other cytokines around a tooth during orthodontic force application to produce localized bone remodelling around an orthodontically moving tooth. It is at this level that the LED phototherapy was expected to have an effect.

B) The split-mouth design and the possibility of a systemic effect of LED phototherapy

Pilot studies by the manufacturer have shown that light from the LED device penetrates into the alveolus (see Material and Methods). Regarding the possibility of photoleakage, previous studies investigating tissue absorption of “red” and “near infrared” light in a variety of human tissue have demonstrated that the spectroscopic absorption penetration was less than 4.23mm (Stolik et al., 2011; Stolik et al., 2000). Although this depth of penetration may seem inadequate, it is known that photodynamic therapy includes not only the photochemical reaction but also local increases in tissue temperatures and that thermal penetration exceeds that of spectroscopic penetration. However, assessment of the depth of thermal penetration in a variety of human tissues has shown that light induced increases in tissue temperatures decrease exponentially with distance from the light source and that at a distance of 20mm, which is less than the distance to the midline of the mouth, thermal increases were 0.2 degrees Celsius (Stolik et al., 2011, Stolik et al., 2000).

Given that the LED device is known to penetrate the alveolus and that OTM is a metabolic phenomenon limited to the immediate area around a moving tooth, this study’s experimental design was consistent with the a biostimulatory (a.k.a. phototherapeutic) window (Sommer et al., 2001) whereby the energy delivered to the tissue to produce an effect must lay within a desired range. Furthermore, this approach is one that has been used in clinical studies
on the effect of LLLT (Genc et al., 2012; Doshi-Mehta and Bhad-Patil, 2011; da Silva Sousa et al., 2009; Kocoglu-Altan et al., 2009; Youssef et al., 2008; Limpanickul et al., 2006; Cruz et al., 2004), local delivery of prostaglandins (Seifi et al. 2003; Spielmann et al., 1989) and pulsed electromagnetic field (Showkatbakhsh et al., 2010) to assess the rate of OTM. It is on these reasons that this study relied on the ability of the split mouth design to provide an adequate control for the implementation of the LED application. The reliability of this deduction can be seen in the finding of an average rate of OTM of 1.2mm/month in both groups, a rate that is within the expected normal rate of OTM of 0.76-2.044mm/month (Youssef et al., 2008), illustrating no overall increase or decrease in the rate of OTM in comparison to prior studies of similar nature and thereby validating a lack of a systemic effect of LED phototherapy.

4.3 Biomechanical Considerations in the Evaluation of the Rate of Orthodontic Tooth Movement

In evaluating the rate of OTM it is important to acknowledge that dental tipping is known to occur more easily than bodily movement (Proffit et al., 2007). As such, it is reasonable to expect that dental tipping could contribute to the reduction in extraction space closure if biomechanics to limit dental tipping and encourage bodily movement were not employed. In this study active space closure via bodily movement of the teeth was encouraged by the use of an adequately rigid arch wires and a space closing force that would not overpower the biomechanical system intended to prevent unwanted tooth movement (i.e., excessive orthodontic dental tipping) over a 3 month period of extraction space closure. A force of 150g was delivered from constant force nickel titanium coil springs on stainless steel wires equal to or larger than 0.018” or 0.016x0.022” in dimension to produce an average OTM of 0.04mm/d
Similar biomechanical protocols to the one used in this study have been reported to produce dental tipping limited to <11° over the 2 months study period during canine retraction (Cruz et al., 2004). The force level used in this study and the observed OTM were comparable to most of the studies reported in the literature. For example, a generally accepted level of force of 150g has been reported to produce movement of 0.76-2.044mm/mos, with the majority reported between 0.076-1.064mm/month (Youssef et al., 2008). It has also been reported that 150g and 200g of force from nickel titanium (NiTi) coils were similar in their efficiency at space closure and that this method was equivalent in efficiency to elastomeric powerchain but more efficient than closing loops (Barlow and Kula, 2008). The choice of 150g of force represents the upper range of acceptable force level for single tooth (eg. canine) retraction to facilitate frontal resorption and is consistent with the force levels used in prior studies showing the effect of LLLT on OTM (Doshi-Mehta and Bhad-Patil, 2011; da Silva Sousa et al., 2009; Youssef et al., 2008; Proffit et al., 2007; Masella and Meister, 2006; Cruz et al., 2004). To account for the possibility that the change in extraction space over time with OTM was affected by hyalinization, the data analysis was performed with considerations for temporal variations in OTM (see Results, Figures 3.4, 3.5 & 3.6). However, these analyses did not show any differential effects on the rate of OTM with time, indication that significant hyalinization did not hinder the rate of OTM in this study.

This study illustrated that IR-LED phototherapy did not appear to have any significant effect on the rate of OTM in the sample population in this study. The results were consistent with 2 similar human studies, but contrasted with some other studies where LLLT was used to accelerate tooth movement (Genc et al., 2012; Doshi-Mehta and Bhad-Patil, 2011; da Silva Sousa et al., 2009; Kocoglu-Altan et al., 2009; Youssef et al., 2008; Limpanichkul et al., 2006; Cruz et al., 2004).
An analysis of the rates of OTM observed in this study showed that the observed rate of 1.2mm/mos of OTM for both control and LED treated teeth were consistent with previously published effects of LLLT on OTM and on OTM in general. This finding demonstrates that the patients of this study and the mechanics used for extraction space closure were consistent and comparable with that of previous literature.

A close analysis of the OTM rates showed that the study sample had a wide range of starting extraction space sizes when categorized by those treated on round wires versus rectangular wires. This finding was not of importance as it was the rate of OTM (the slope of the lines in Results, Figure 3.4) that was determined to not show any difference from the LED phototherapy application. Further analysis also demonstrated that one LED phototherapy treated canine did not exhibit space closure during the T0-T1 phase. This observation was not expected. It is possible that the orthodontic biomechanics of this patient were altered by influences beyond the control of the study. It is possible that friction levels between the archwire and bracket (eg., from accumulations of calcified food debris or distortions of the orthodontic wire) may have been increased momentarily, preventing tooth movement. However, this patient subsequently showed tooth movement in the T1-T2 treatment phase. Perhaps this patient underwent an unusually long hyalinization period once a retraction force was applied to the tooth. However, this would not be expected as this phenomenon was not seen on the control side. In an attempt to account for this data as illegitimate, a separate data analysis was done without this data set. This did not alter the findings of no effect of IR-LED phototherapy on the rate of OTM and thus was not removed from the total sample.
4.4 Possible Reasons for the Lack of Effect of LED on Rate of OTM

This study showed that IR-LED phototherapy did not appear to have any significant effect on the rate of OTM in the sample population in this study. The results were consistent with 2 similar human studies, but contrasted with some other studies, where LLLT was used to accelerate tooth movement (Genc et al., 2012; Doshi-Mehta and Bhad-Patil, 2011; da Silva Sousa et al., 2009; Kocoglu-Altan et al., 2009; Youssef et al., 2008; Limpanichkul et al., 2006, Cruz et al., 2004).

A number of factors might be responsible for the lack of differences from LED phototherapy in this study.

A) Dosage of LED:

The patients were asked to apply the LED device once per day between orthodontic appointments. It is possible that the dose received (ie. the IR-LED intensity or duration) was inadequate or in excess to cause a notable effect on OTM. Such a scenario would indicate that the current dosage was insufficient to enter a phototherapeutic window. A consequence of being outside of this therapeutic range would be no biological effects, an explanation that has been cited in prior LLLT studies that did not demonstrate a benefit to laser therapy on OTM (Kocoglu-Altan, 2009; Limpanichkul et al., 2006) and in studies where phototherapeutic effects have been seen at only one of two energy levels (Goulart et al., 2006).

If it is assumed that the LED device settings were appropriate, then attenuation of the LED light is another possibility for a reduced dose-response effect. IR-LED light is primarily scattered and absorbed by skin pigmentation and hemoglobin but this attenuation can be reduced by the use of longer infrared wavelengths (Graber et al., 2012; Stolik et al., 2011; Stolik et al.,
Although it is possible that the thickness of the soft tissues of the cheek interfered with the light penetration into the alveolar tissue, preliminary studies by the manufacturer of the LED device have shown that the LED light does penetrate the cheek adequately to reach the alveolar bone (see device settings description in the Materials and Methods). Also, studies have shown that thermal penetration is relatively constant despite differences in light penetration, resulting in a given volume of tissue showing phototherapy-induced thermal changes in excess of the volume of tissue that had absorbed light (Stolik et al., 2011).

**B) LED device compliance**

Another possibility for the lack of observable effects of LED phototherapy on OTM is that patient compliance was unacceptable. The study protocol relied on 2 measures to account for compliance. The first method used a data log in the LED device. This mechanism only recorded completed LED phototherapy cycles. Furthermore, the device has face detection software that detected light reflected from the skin once the LED arrays were in place. This ensured that the device was used. To augment the compliance data, a manual log was kept by each patient. These manual logs matched perfectly with the device logs, confirming that the compliance rate was accurate. The results indicated that on average, patients completed the prescribed LED phototherapy protocol with an 80% success rate. This rate is within the recommendations of the manufacturer who at a minimum requested use every other day, if not for the idea regime of once per day. In other words, the proposed therapeutic window was between 50-100% compliance of the prescribed usage. This is consistent with previous proposals which state that it is the total amount of phototherapy received that is essential to induce biostimulation (Abi-Ramia et al., 2010; Kim et al., 2009) but also that a certain energy
threshold must be met for a biostimulatory effect to be seen—i.e., The Arndt-Schultz Law (see Introduction, Figure 1.1) (Kim et al., 2009). However, it is not known if the dose and/or duration of light received at each light exposure in this study contributed to biostimulation. Furthermore, it is possible that the therapeutic range was incorrect and that a shorter or longer total LED exposure either on a daily basis or occurring from earlier on in orthodontic treatment could yield an effect on OTM.

C) Temporal effect of LED phototherapy

With respect to the cumulative effect of LED phototherapy, the literature on the temporal effects of phototherapy is limited. Da Sousa Silva et al. (2011) described a decreasing trend of effectiveness of laser therapy on the rate of OTM in a 3 month clinical study but their canines were retracted on a less rigid wire than in this study and would therefore be more susceptible to dental tipping, a potentially complicating variable in the assessment of OTM. However, others have cited a peak OTM velocity at 7 of 8 weeks of laser therapy in dogs (Kim et al., 2009). To assess if the total LED light received had any effect, the average rates of OTM at days 20, 45, 60 and 80 as a function of total LED received were extrapolated and analyzed. This analysis did not indicate any significant difference in OTM rates with IR-LED phototherapy, suggesting that the cumulative effect of the LED was not influential on OTM over a 3 month period. These findings also indicated that any initially contributions of dental tipping as a confounding variable in the rate of OTM were controlled for by the biomechanical protocol.

D) Age and sex dependent effects of LED phototherapy

Although LLLT has been shown to increase the rate of OTM, no prior studies on IR-LED-mediated phototherapy have been reported in humans. It was possible that alterations in
OTM may have been linked to an LED phototherapeutic effect which was dependent on age or sex. The data and statistical analysis included the factors of age and sex as potential contributing variables but no significant effects were found. In this study the average age of the patient population and sex distribution indicate that the study sample would be expected to be peripuberal and of a relatively high metabolic activity (in contrast to an older adult population). It is well known that metabolism and cellular activity changes with increased age and that pubertal hormone changes occur during teenage years. Studies have shown these changes as well as increases in fibrosis and decreases in elasticity within periodontal tissues (Ryan et al., 1974; Reitan et al., 1985 & 1964). Given that studies looking at the effect of LED phototherapy and LLLT have credited biostimulatory effects to increases in cell metabolism, activity and proliferation with therapeutic benefits in tissue repair and OTM, it may be possible that the patient sample demonstrated an already high metabolism that would not show a significant benefit from the biostimulatory effects of the LED phototherapy. If this were the case the findings of this study would suggest that LED phototherapy has different effects from LLLT or that variations in dose of concentration can produce different biological effects. Also, another possibility could be that the effect of LED phototherapy would be appreciated in an older patient population whose metabolic rate is lower than that of a younger individual.

4.5 Future Directions

Although well designed, this study was challenged by logistical limitations in patient recruitment and a lack of a known dose-effect relationship of the LED phototherapy and phototherapy as a whole. The results indicate that the rate of OTM was very similar between the control and IR-LED phototherapy treated groups. A larger sample size would permit more
thorough understanding of the influence of such factors as age, as well as provide a larger data set for other statistical modelling in consideration of patient specific variables (eg. sex, which teeth where undergoing retraction, LED-device compliance and dose-effect relationships). In addition to a larger sample size, the assessment of changes in extraction space size at more frequent time points would facilitate a better understanding of any temporal changes in OTM as extraction spaces are closed and if LED phototherapy has time-dependent effects. This extension of the number of visits to the study protocol, although challenging from an ethical and clinical management standpoint, would give insights into if IR-LED phototherapy is beneficial during certain phases of OTM and therefore orthodontic treatment.

4.6 CONCLUSIONS

The results of this study showed that extra-orally derived, transdermal IR-LED phototherapy could be prescribed with a high degree of patient compliance. However, IR-LED phototherapy was not found to affect the rate of OTM during the first three months of active extraction space closure in a split mouth design.
Chapter 5: ACCEPTED ABSTRACTS

5.1 Abstract for poster presentation in the Clinical Sciences category-Faculty of Dentistry, University of Toronto in February 2013.

The Role of Light Emitting Diode Phototherapy (LED) in Orthodontic Tooth Movement (OTM).

S CHUNG*, S GONG, B TOMPSON.

Department of Orthodontics, Faculty of Dentistry, University of Toronto

Objective: An increase in orthodontic treatment efficiency has been reported with laser application. However, lasers require a controlled clinical environment for safe and effective delivery. This study will investigate if light emitting diode (LED) phototherapy is a viable alternative. Results from our study will offer clues to the potential use of LED to accelerate the rate of orthodontic tooth movement (OTM) in the clinical setting.

Methods: Eleven patients undergoing orthodontic treatment at the Faculty of Dentistry, UT, were selected. Inclusion criteria included bilaterally symmetric extraction of premolars and full banding and bonding of appliances. During space closure of the extraction site, LED phototherapy was applied to one side of the dental arch for 20 minutes daily for 4-12 weeks. LED phototherapy was recorded by the LED unit as well as by the patient. To permit measurements of space closure on dental casts, dental impressions were taken at 3 time points using a chromatic alginate with long dimensional stability (Kromopan) immediately prior to (T0), during (T1) and after space closure (T2). The rate of space closure of the control and LED treated sides were compiled and compared with each other.

Results: All eleven patients were compliant with LED application. On average the duration of usage was 78% at T1 and 82% at T2. Preliminary results suggest that no significant differences resulted from the application of LED phototherapy.

Conclusions: The results suggest that extra-orally delivered LED phototherapy does not significantly alter the rate of OTM. This is to contrary previous findings with laser phototherapy.
mediated modulation of OTM and could be related to the duration or method of LED delivery. Further investigations are needed to determine whether LED phototherapy application can influence the rate of OTM.

**Supported by:** University of Toronto, Faculty of Dentistry Dental Research Institute
The Role of Light Emitting Diode (LED) Phototherapy on Orthodontic Tooth Movement (OTM).

S CHUNG*, S GONG, B TOMPSON.

Department of Orthodontics, Faculty of Dentistry, University of Toronto

Objective: This study investigated LED phototherapy as an alternative to lasers in accelerating the rate of OTM in the clinical setting (Faculty of Dentistry, University of Toronto).

Methods: During space closure of bilaterally symmetric premolar extraction sites, LED phototherapy was applied to one side of the dental arch (20 min/d; 4-12 weeks). Extraction spaces were measured on dental casts taken before (T0), during (T1) and later in space closure (T2). LED usage was recorded by the patient and the device. The rates of space closure in controls and LED-treated sides were compared.

Results: All patients were compliant with LED usage. Preliminary results suggest no significant differences with the application of LED phototherapy.

Conclusions: Preliminary results suggest that extra-orally delivered LED phototherapy does not significantly alter the rate of OTM. Further studies are needed to determine if variations in the LED phototherapy prescription can influence the rate of OTM.

Supported by: U of T, Faculty of Dentistry Dental Research Institute
5.3 Abstract for poster presentation in the Canadian Association of Orthodontists (CAO) Annual Scientific Meeting in September 2013 in Banff, Alberta.

The Role of Light Emitting Diode Phototherapy (LED) in Orthodontic Tooth Movement (OTM).

S CHUNG*, S GONG, B TOMPSON.

Department of Orthodontics, Faculty of Dentistry, University of Toronto

Objective: An increase in orthodontic treatment efficiency has been reported with laser application. However, lasers require a controlled clinical environment for safe and effective delivery. This study will investigate if light emitting diode (LED) phototherapy is a viable alternative. Results from our study will offer clues to the potential use of LED to accelerate the rate of orthodontic tooth movement (OTM) in the clinical setting.

Methods: Eleven patients undergoing orthodontic treatment at the Faculty of Dentistry, UT, were selected. Inclusion criteria included bilaterally symmetric extraction of premolars and full banding and bonding of appliances. During space closure of the extraction site, LED phototherapy was applied to one side of the dental arch for 21 minutes daily for 4-12 weeks. LED phototherapy was recorded by the LED unit as well as by the patient. To permit measurements of space closure on dental casts, dental impressions were taken at 3 time points using a chromatic alginate with long dimensional stability (Kromopan) immediately prior to (T0), during (T1) and after space closure (T2). The rate of space closure of the control and LED treated sides were compiled and compared with each other.

Results: All eleven patients were compliant with LED application. On average the duration of usage was 78% at T1 and 82% at T2. Preliminary results suggest that no significant differences resulted from the application of LED phototherapy.

Conclusions: The results suggest that extra-orally delivered LED phototherapy does not significantly alter the rate of OTM. This is to contrary previous findings with laser phototherapy mediated modulation of OTM and could be related to the duration or method of LED delivery. Further investigations are needed to determine whether LED phototherapy application can influence the rate of OTM.
References


Brawn, P. R., & Kwong-Hing, A. (2007). Histologic comparison of light emitting diode phototherapy-treated hydroxyapatite-grafted extraction sockets: A same-mouth case study. *Implant Dentistry, 16*(2), 204-211. doi: 10.1097/ID.0b013e318065a84c


APPENDIX A:

A1. Scientific merit approval from the Dental Research Institute, Faculty of Dentistry-
University of Toronto.

Ref. # 11-12-2

September 29, 2011

Dr. Bryan Tompson
Faculty of Dentistry
University of Toronto

Dear Bryan,

Your revised application entitled “The effect of light emitting diode (LED) phototherapy on orthodontic tooth movement in humans.” was assessed by the Research Committee and 2 referees. Your project is now approved for scientific merit and funding for the amount of $2,640.00.

Please read the attached Faculty grant guidelines carefully and address any issues directly with Ms. Leah Raz. Leah will set up the account for your research project and provide you with the appropriate instructions for accessing the funds.

I wish to also remind you that in accordance with the grant policy, you must submit a one page project report, which will also include as an attachment, a list of any documents produced by the applicants or trainee(s) (i.e. Research Committee presentations, abstracts, papers, thesis, etc.), and/or submitted funding applications to external agencies, that were directly related to the Dental Faculty Research Grant (DFRG) funding. The report is to be submitted within 6 months following one year from the date of funding allocation (i.e. 18 months following receipt of funding).

Any unspent funds remaining in the account after one year from the funding date will be returned to the research fund pool. If you will require an extension on the work for reasons that were beyond your control you must make your request in writing, addressed to the Associate Dean Research, c/o Leah Raz, Dental Research Institute, prior to 1 month of the termination date for your grant.

I wish you all the best in this study and I am looking forward to seeing the results at the Faculty’s Annual Research Day.

Sincerely,

Leah Raz for
Dr. Bernhard Ganss
Associate Dean (Research)

Cc: Dr. Siew-Ging Gong
Dr. Sean Chung

124 Edward Street
Toronto Ontario M5G 1G6
FAX (416) 979-4770
A2. Ethics approval from the Research Ethics Board, University of Toronto.

PROTOCOL REFERENCE # 26641

July 13, 2011

Dr. Bryan Tompson & Dr. Slew-Ging Gong
Faculty of Dentistry
University of Toronto
124 Edward St.
Toronto, ON M5G 1G6

Dr. Sean Chung
Faculty of Dentistry
University of Toronto
124 Edward St.
Toronto, ON M5G 1G6

Dear Drs. Tompson, Gong and Chung:

Re: Your research protocol entitled, “The effect of light emitting diode (LED) phototherapy on orthodontic tooth movement in humans”

ETHICS APPROVAL

Original Approval Date: July 13, 2011
Expiry Date: July 12, 2012
Continuing Review Level: 1

We are writing to advise you that the Health Sciences Research Ethics Board has granted approval to the above-named research study under the REB’s delegated review process. Your study has been approved for a period of one year and ongoing projects must be renewed prior to the expiry date.

All your most recently submitted documents have been approved for use in this study.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events should be reported to the Office of Research Ethics as soon as possible.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 15 to 30 days prior to the expiry date of your study. Note that annual renewals for studies cannot be accepted more than 30 days prior to the date of expiry, as per federal and international policies.

If your research has funding attached, please contact the relevant Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your project.

Yours sincerely,

Daniel Gyewu
Research Ethics Board Manager - Health Sciences

OFFICE OF RESEARCH ETHICS
McMurrich Building, 12 Queen's Park Crescent West, 2nd Floor, Toronto, ON M5S 3S8 Canada
Tel: +1 416 946-3277 • Fax: +1 416 946-5763 • ethicsreview@utoronto.ca • http://www.research.utoronto.ca/for-researchers-administrators/ethics/
UNIVERSITY OF
TORONTO

PROTOCOL REFERENCE # 26641

June 29, 2012

Dr. Bryan Tompson and Siow-Ging Gong
FACULTY OF DENTISTRY

Sean Chung
FACULTY OF DENTISTRY

Dear Dr. Bryan Tompson, Siow-Ging Gong and Sean Chung,

Re: Your research protocol entitled, "The effect of light emitting diode (LED) phototherapy on orthodontic tooth movement in humans"

ETHICS APPROVAL

Original Approval Date: July 13, 2011

Expiry Date: July 12, 2013

Continuing Review Level: 1

Renewal: 1 of 4

We are writing to advise you that you have been granted annual renewal of ethics approval to the above-referenced research protocol through the Research Ethics Board (REB) delegated process. Please note that all protocols involving ongoing data collection or interaction with human participants are subject to re-evaluation after 5 years. Ongoing research under this protocol must be renewed prior to the expiry date.

Please ensure that you submit an Annual Renewal Form or a Study Completion Report 15 to 30 days prior to the expiry date of your protocol. Note that annual renewals for protocols cannot be accepted more than 30 days prior to the date of expiry as per our guidelines.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events should be reported to the Office of Research Ethics as soon as possible. If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Best wishes for the successful completion of your research.

Yours sincerely,

Judith Friedland, Ph.D.
REB Chair

Daniel Gyewu
REB Manager

OFFICE OF RESEARCH ETHICS

McMaster Building, 11 Queen's Park Crescent West, 2nd Floor, Toronto, ON M5S 1A8 Canada
Tel: +416 946 8733 Fax: +416 946 9769 ethics.review@utoronto.ca http://www.research.utoronto.ca/ethics/
CONSENT FOR TREATMENT

I hereby give consent to the Faculty of Dentistry, University of Toronto, to provide basic preliminary dental care, the need for and the cost of which will be explained to me before it is delivered. This may include teeth cleaning, specific investigations, preventive advice and the treatment of decayed or infected teeth. This may also include the taking of records, radiographs and photographs (which may be used for teaching and publication purposes and may not be left anonymous) and the administration of necessary anaesthetics and medications. I also understand that this treatment will be done by students only, as part of their learning process.

I hereby give consent for the Faculty of Dentistry, University of Toronto, and its students and residents to use patient treatment records and other patient clinic information, including, for example, diagnostic information, x-rays and photos of treatment outcomes for academic and accreditation purposes such as teaching, publication and examinations, including those undertaken after graduation and/or outside the University of Toronto. Photos of treatment outcomes may show the patient’s face.

I have also read and understand the Clinic Policies and Regulations printed on the previous page and agree to abide by them.

As to fees for these services, I agree to make payments as treatment progresses except for those procedures requiring laboratory services. For these services, I shall pay at least one-half the total fee before the treatment is begun and the balance before insertion of the restoration. I am also aware that there may have to be revisions in costs for treatment of long duration. These revisions will be discussed with me before the treatment is begun.

Signature of Patient: ___________________________ Date: ___________________________
(Parents or guardian must sign for dependents or patients under 18 years of age)

Signature of Witness: ___________________________ Date: ___________________________
FACULTY OF DENTISTRY
CLINIC POLICIES AND REGULATIONS FOR PATIENTS

1. A limited number of patients are accepted in our Faculty Clinic based on their suitability for teaching purposes.

Not everyone is suitable to become or remain a patient. The following criteria indicate unsuitability:

- Extensive and/or complex dental treatment is required
- Patient management challenges are beyond the capability of an undergraduate student
- Complex medical history
- Dental treatment needs are not compatible with our educational programme
- A combination of any of the above criteria

Prospective patients are reviewed on entry to the Faculty clinics and periodically thereafter. If at any stage in their treatment, based on the above criteria, they are found to be unsuitable to be treated in the Faculty clinics, they may be asked to seek dental care in an alternative facility. Please be assured that these decisions are taken in the best interests of both the patient and the students of the Faculty of Dentistry.

2. Treatment of accepted patients may not begin immediately, since patients are assigned to students at times during the year to correspond with their course of study.

3. All treatment will be provided by students who have other patients and assignments as well. Progress may be slow; therefore completion of treatment cannot be assured within a specific time.

4. Fees quoted are estimates only and subject to change for treatment of long duration. Patients will be advised of any changes to the estimate prior to providing treatment. It is required that payment be made at each visit.

5. Patients who have a dental insurance plan or are receiving social assistance should make this known at their first appointment. For those with dental insurance, required payment must be made to the Faculty first and the specific treatment finished before a claim form is completed.

6. Patients must be willing to attend our clinic at least once a week at times required by the student; that is:- 9:45 a.m. to 12:45 p.m. or 1:45 p.m. to 4:45 p.m. Monday to Friday. This does not mean that a patient will be coming every week necessarily but must be willing to do so. Patients must be prepared to spend a half-day for each appointment.

7. Appointments must be kept punctually. Twenty-four hours notice must be given if cancellation or change of appointment is necessary, as poor patient attendance will result in dismissal from the clinic.

8. Parents may attend with their children who are receiving dental care provided the supervising staff member has given them permission and they agree to follow the rules of conduct as presented by the student/instructor. If they do not follow the rules of conduct as presented they may then be asked to leave the clinic and wait in the reception area. If they refuse to do this we will discontinue the treatment of their child and refer them to an outside practitioner.

9. Children are not allowed in adult clinic areas with parents who are receiving treatment and are not allowed in waiting areas unattended.

10. Parents are required to provide supervision, at all times, for children not being treated.

11. Patients unable to speak or understand English must be accompanied by an interpreter at every appointment.

12. Patients who require the use of a wheelchair must either be physically able to transfer themselves to and from the dental chair from the wheelchair for their appointments or must have with them a person or persons who are able to complete the transfer for them. Our staff and students are not able to transfer patients to or from wheelchairs.

13. Treatment will be discontinued if any patient does not comply with the above regulations.
Office of the Assistant Dean, Clinics
Faculty of Dentistry
University of Toronto

PATIENT CONSENT FORM:
FOR COLLECTION, USE AND DISCLOSURE
OF PERSONAL INFORMATION

Privacy of your personal information is an important part of our Faculty providing you with quality dental care. We understand the importance of protecting your personal information. We are committed to collecting, using and disclosing your personal information responsibly. We also try to be as open and transparent as possible about the way we handle your personal information. It is important to us to provide this service to our patients.

In this office, Dr. Luciano Valenzano, Assistant Dean, Clinics acts as the Privacy Information Officer.

All staff members who come in contact with your personal information are aware of the sensitive nature of the information that you have disclosed to us. They are all trained in the appropriate uses and protection of your information.

Attached to this consent form, we have outlined what our office is doing to ensure that:
- only necessary information is collected about you;
- we only share your information with your consent;
- storage, retention and destruction of your personal information complies with existing legislation, and privacy protection protocols;
- our privacy protocols comply with privacy legislation, standards of our regulatory body, the Royal College of Dental Surgeons of Ontario, and the law.

Do not hesitate to discuss our policies with me or any member of our staff.

Please be assured that every staff person in our office is committed to ensuring that you receive the best quality dental care.

How Our Office Collects, Uses and Discloses Patients' Personal Information

Our office understands the importance of protecting your personal information and will at all times protect it in accordance with applicable privacy legislation. To help you understand how we are doing that, we have outlined here how our office is using and disclosing your information.

This Faculty will collect, use and disclose information about you for the following purposes:
- to deliver safe and efficient patient care
- to identify and to ensure continuous high quality service
- to assess your health needs
- to provide health care
- to advise you of treatment options
- to enable us to contact you
- to establish and maintain communication with you
- to offer and provide treatment, care and services in relationship to the oral and maxillofacial complex and dental care generally
- to communicate with other treating health-care providers, including specialists and general dentists who are the referring dentists and/or peripheral dentists
- to allow us to maintain communication and contact with you to distribute health-care information and to book and confirm appointments
- to allow us to efficiently follow-up for treatment, care and billing
- for teaching and demonstrating purposes on an anonymous basis
- for research and publication purposes on an anonymous basis
- to complete and submit dental claims for third party adjudication and payment

124 Edward Street  Toronto Ontario  M5G 1G6  FAX (416) 979-4936
• to comply with legal and regulatory requirements, including the delivery of patients’
charts and records to the Royal College of Dental Surgeons of Ontario in a timely fashion, when required,
according to the provisions of the Regulated Health Professions Act
• to comply with agreements/undertakings entered into voluntarily by the member with the Royal College of
Dental Surgeons of Ontario, including the delivery and/or review of patients’ charts and records to the College
in a timely fashion for regulatory and monitoring purposes
• to deliver your charts and records to the dentist’s insurance carrier to enable the insurance company to
assess liability and quantify damages, if any
• to prepare materials for the Health Professions Appeal and Review Board (HPARB)
• to invoice for goods and services
• to process credit card payments
• to collect unpaid accounts
• to assist this office to comply with all regulatory requirements
• to comply generally with the law

The Faculty of Dentistry, University of Toronto, and its students and residents may use anonymous patient
treatment records and other patient clinic information, including, for example, diagnostic information, x-rays and
photos of treatment outcomes for academic and accreditation purposes such as teaching, publication and
examinations, including those undertaken after graduation and/or outside the University of Toronto. Photos of
treatment outcomes may show the patient’s face.

By signing the consent section of this Patient Consent Form, you have agreed that you have given your informed
consent to the collection, use and/or disclosure of your personal information for the purposes that are listed. If a
new purpose arises for the use and/or disclosure of your personal information, we will seek your approval in
advance.

Your information may be accessed by regulatory authorities under the terms of the Regulated Health Professions
Act (RHPA) for the purposes of the Royal College of Dental Surgeons of Ontario fulfilling its mandate under the
RHPA, and for the defence of a legal issue.

Our Faculty will not under any conditions supply your insurer with your confidential medical history. In the event
this kind of a request is made, we will forward the information directly to you for review, and for your specific
consent.

When unusual requests are received, we will contact you for permission to release such information. We may also
advise you if such a release is inappropriate.

You may withdraw your consent for use or disclosure of your personal information, and we will explain the
ramifications of that decision, and the process.

Patient Consent

I have reviewed the above information that explains how your Faculty will use my personal information, and the
steps your Faculty is taking to protect my information.

I know that your Faculty has a Privacy Code, and I can ask to see the Code at any time.

I agree that the Faculty of Dentistry, University of Toronto can collect, use and disclose personal information
about _______________________________ as set out above in the information about the office’s privacy
policies.

______________________________
Signature of Patient or Parent/Guardian

______________________________
Print Name

______________________________
Date

______________________________
Signature of Witness
INTRODUCTION

Privacy of personal information is an important principle in the provision of quality dental care to our patients. We understand the importance of protecting your personal information. We are committed to collecting, using and disclosing your personal information responsibly. We also try to be as open and transparent as possible about the way we handle your personal information.

We have tried to make our office Privacy Code as easy to understand as possible. To ensure that you see how we are complying with the federal privacy legislation, the Personal Information and Protection and Electronic Documents Act (PIPEDA), our Privacy Code is organized to follow the Act's ten interrelated principles that are the foundation of PIPEDA.

DEFINITIONS

Collection – The act of gathering, acquiring or obtaining personal information from any source, including third party sources by any means.

College – Royal College of Dental Surgeons of Ontario

Consent – A voluntary agreement with what is being done or is being proposed to be done. Consent can either be express or implied. Express consent may be given explicitly, either orally or in writing.

Disclosure – Making personal information available to others besides the dentist or the dental team.

Legislation – The Regulated Health Professions Act (RHPA), Schedules attached, Dentistry Act, Regulations made under these Acts, and By-laws of the College, and the Personal Information Protection and Electronic Documents Act (PIPEDA)

Member – A member of the Royal College of Dental Surgeons of Ontario and this includes a health profession corporation

Faculty – The Faculty of Dentistry and when referencing access to information, to the Privacy Information Officer, and the Faculty of Dentistry

Patient – An individual about whom the dentist collects personal information in order to carry out prognosis, diagnosis, and treatment, including controlled acts

Personal Information – Information about a patient that is recorded in any form, and this includes: the patient’s name, address, telephone number, social insurance number, tax number, e-mail address, gender, marital status, children, date of birth, occupation, medical records, health records, insurance company, insurance coverage, history, occupation, place of work, employer

RHPA Procedural Code – The Health Professions Procedural Code, Schedule 2 to the Regulated Health Professions Act (RHPA)

PIPEDA PRINCIPLES

Principle 1: Accountability

Any dentist in this Faculty is responsible for information collected by him/her, or under his/her direction, and under his/her control.

Accountability for this Faculty's compliance rests with the designated individual or individuals, even though others in the Faculty may be responsible for the day-to-day collection and processing of personal information.

The identity of the individual designated by the Faculty to oversee the compliance, the Privacy Information Officer, will be made known upon request.

This Faculty is responsible for information in our possession or custody, including information that has been transferred to a third party for processing. We will use contractual or other means to provide a comparable level of protection while the information is being accessed and/or processed by that third party.

Our Faculty will implement policies and practices to give effect to the principles, including:
• implementing policies to protect personal information;
• establishing procedures to receive and respond to complaints and inquiries;
• training staff about privacy policies and practices;
• developing information to explain privacy policies and procedures.

Principle 2: Identifying Purposes for Collecting Information

The purposes for which personal information is collected in this Faculty will be identified before or at the time the information is collected.

This Faculty collects personal information for the following purposes:
• to deliver safe and efficient patient care
• to identify and to ensure continuous high quality service
• to assess your health needs
• to provide health care
• to advise you of treatment options
• to enable us to contact you
- to establish and maintain communication with you
- to offer and provide treatment, care and services in relationship to the oral and maxillofacial complex and dental care generally.
- to communicate with other treating health-care providers, including specialists and general dentists who are the referring dentists and/or peripheral dentists
- to allow us to maintain communication and contact with you to distribute health-care information and to book and confirm appointments
- to allow us to efficiently follow-up for treatment, care and billing
- for teaching and demonstrating purposes on an anonymous basis
- for research and publication purposes on an anonymous basis to complete and submit dental claims for third party adjudication and payment
- to comply with legal and regulatory requirements, including the delivery of patients' charts and records to the College in a timely fashion, when required, according to the provisions of the Regulated Health Professions Act
- to comply with agreements/undertakings entered into voluntarily by the member with the Royal College of Dental Surgeons of Ontario, including the delivery and/or review of patients' charts and records to the College in a timely fashion for regulatory and monitoring purposes
- to deliver your charts and records to the dentist's insurance carrier to enable the insurance company to assess liability and quantify damages, if any
- to prepare materials for the Health Professions Appeal and Review Board (HPARB)
- to invoice for goods and services
- to process credit and debit card payments
- to collect unpaid accounts
- to assist this office to comply with all regulatory requirements
- to comply generally with the law

This Faculty will identify the purposes for which personal information is collected, at or before the time of collection. We will only collect that information necessary for the identified purposes.

When personal information has been collected and is to be used or disclosed for a purpose not previously identified, the new purpose will be identified prior to its use or the disclosure. Your consent is required before the information can be used or disclosed for that purpose.

Faculty staff collecting personal information will be able to explain to you the purpose for which the information is being collected.

When you sign the Patient Consent Form, you will be deemed to understand and accept this office’s collection, use and disclosure of your information for the specified purposes.

Principle 3: Consent

This Faculty will seek informed consent for the collection, use and/or disclosure of personal information, except where it might be inappropriate to obtain your consent, and subject to some exceptions set out in law.

Consent is required for the collection of personal information and subsequent use or disclosure of that information.

In order for the principles of consent to be satisfied, our office has undertaken reasonable efforts to ensure that you are advised of the purposes for which information is being used, and that you understand those purposes. Once consent is obtained, we do not need to seek your consent again, unless the use, purpose or disclosure changes.

Existing protocols for electronic submissions of dental claims require a signature on file. Specific consent may be required for additional requests from insurers. This shall be collected at the time, or in conjunction, with predeterminations for extensive services, providing the scope of information released is disclosed. If there is any doubt, information shall be released directly to you for review and submission.

Consent for the collection, use and disclosure of personal information may be given in a number of ways, such as:
- signed medical history form;
- signed introductory questionnaire;
- taken verbally over the telephone and then charted;
- e-mail;
- written correspondence.

You may withdraw consent upon reasonable notice.

Principle 4: Limiting Collection of Personal Information

The collection of personal information by our office shall be limited to that which is necessary for the purposes identified in this Privacy Code.

Principle 5: Limiting Use, Disclosure and Retention

Personal information shall not be used or disclosed for purposes other than those for which the information is collected, except with your express consent, or as required by law.

Our Faculty has protocols in place for the retention of personal information.

Retention of information records is defined and referenced in College's Guidelines on Dental Recordkeeping.

In destroying personal information, our Faculty has developed guidelines to ensure secure destruction in accordance with the College's Guidelines on Dental Recordkeeping.
Principle 6: Accuracy of Personal Information
This Faculty endeavours to ensure that your personal information is as accurate, complete, and as up-to-date as necessary for the purposes that it is to be used.

The extent to which your personal information shall be accurate, complete and up-to-date will depend upon the use of the information, taking into account the interest of our patients.

Information shall be sufficiently accurate, complete and up-to-date to minimize the possibility that inappropriate information is used to make a decision about you as our patient.

Principle 7: Safeguards for Personal Information
Our Faculty has taken appropriate measures to safeguard your personal information from unauthorized access, disclosure, use or tampering.

Safeguards are in place to protect your personal information against loss or theft, as well as unauthorized access, disclosure, copying, use or modification.

Your information is protected, whether recorded on paper or electronically.

Our staff and students are aware of the importance of maintaining the confidentiality of personal information.

Care is used in the care and destruction of personal information to prevent unauthorized access to the information even during disposal and destruction.

Principle 8: Openness about Privacy
Our Faculty will make readily available to you specific information about our Faculty policies and practices relating to the management of personal information.

This information includes:
• a Patient Information Sheet that outlines the name of the Privacy Information Officer who is accountable for our Faculty privacy policies. This is the person to whom you can direct any questions or complaints. The Information Sheet also describes how to access your personal information held in this office;
• a copy of our Patient Consent Form that explains how this Faculty collects, uses and discloses your personal information;
• our Office Privacy Code.

Principle 9: Patient Access to Personal Information
Upon written request and with reasonable notice, you shall be informed of the existence, use and disclosure of your personal information, and shall be given access to that information.

Upon written request and with reasonable notice, our Faculty will advise you whether or not we hold personal information about you.

Our Faculty shall allow you access to this information. Upon written request and with reasonable notice, our Faculty shall provide you with an accounting of how your personal information has been used, including third party disclosures. In providing this information, we will attempt to be as specific as possible.

When it is not possible to provide a list of the organizations or individuals to which there has been disclosure about you, we will provide you with a list of such organizations or individuals to which we may have disclosed information about you. Disclosure of probabilities in these cases would satisfy this requirement.

We will respond to your request within a reasonable period of time, and at minimal or no cost to you. The request for information will be provided or made available in a form that is generally understandable.

The dentist will comply with the regulations of his/her College that define patient access to records.

You are free to challenge the accuracy and completeness of the information and seek to have it altered, amended, or changed. This process is explained in the Patient Information Sheet.

When a challenge is not resolved to your satisfaction, we will record the substance of the unresolved challenge.

When appropriate, the existence of the unresolved challenge shall be transmitted to third parties having access to the information in question. This disclosure may be appropriate where a dentist has been challenged about a change to a service date or services rendered under consideration for insurance benefits.

Principle 10: Challenging Compliance
You shall be able to challenge compliance with these principles with the Faculty’s Privacy Information Officer who is accountable within the dental office for the dentist’s compliance. Our Faculty has in place procedures to receive and respond to your complaints or inquiries.

This information, including the name of our Faculty’s Privacy Information Officer, is included in the Patient Information Sheet, available on request.

The procedures are easily accessible and simple to use.

Our Faculty has an obligation to inform our patients who make inquiries about how to access the privacy complaint process in our Faculty, and about how to access that process. This information is outlined in the Patient Information Sheet.

The Privacy Information Officer in our Faculty will investigate each and every complaint made to the office in writing.

If a complaint is found to be justified, the Privacy Information Officer will take appropriate measures, including, if necessary, amending any office policies and practices.

Patients will be provided with information about how to contact the Privacy Commissioner of Canada to forward any unresolved complaint. This information is included in the Patient Information Sheet, available on request.
A4. Biolux Light Emitting Diode Device Description

Biolux LED device System

Introduction
Manufacturer Information
Biolux Research Ltd.
825 Powell Street, Suite 220
Vancouver BC, Canada
V6A 1H7
Toll Free: 888.669.0674
Tel: 604.669.0674
Fax: 604.608.5558
www.Bioluxresearch.com

Device Identification

Device Description

The Biolux LED device is a low level LED phototherapy device intended to provide stimulation for accelerating orthodontic movement of teeth. The light is produced by Light Emitting Diodes which are small, efficient semiconductor devices used in many medical and dental applications. The Biolux LED device has a near infrared wavelength of 850 nm, very low level power (less than 50 mW/cm²), and a divergent beam. All light treatment is provided extra-orally, and, other than potentially accelerating the treatment time, at no point are the normal orthodontic treatments, procedures, or appliance altered or affected.

Biolux has determined the Biolux LED device to be a Class 1M device in accordance with IEC 60825-1 “Safety – Part 1: Equipment classification, requirements and user’s guide”, and are therefore deemed “safe under reasonably foreseeable conditions.” No optics or magnifiers are employed with the beam.

The United States Food and Drug Administration on August 18, 2010 advised us that our device and protocol is considered an NSR (Non significant risk).
The Biolux LED device is meant to be operated under the dentist prescription and to be used by the eligible patients in a home setting according to preset frequency and intensity. The Biolux LED device consists of three main components:

1. A stationary **LightPod™ Controller** (see Figure 1), which houses the microprocessor, the menu driven software and the LCD screen. The Controller plugs into the power mains via a medically approved, UL certified (to CSA 60601-1) isolation transformer, which reduces the operating voltage to 24V and the leakage current to less than 10 µA.

2. An **Extra-Oral Mini-Array** connected to the Controller and mounted on the Face Frame (see Figure 2).

3. A **Face Frame**, similar to an eyeglass support structure, to be worn by the patient and hosting the Mini-Array (see figure 2)

**Figure 1** – LightPod™ Controller

![Figure 1](image1.png)

**Figure 2** – Biolux LED device in Situ on Patient

![Figure 2](image2.png)

The Biolux LED device does not contain animal tissue or derivatives, is non-sterile, does not emit ionizing radiation, does not contain pharmaceuticals, and does not store or channel blood or body liquids. The device is an active stationary equipment, powered by the supply mains via a medically approved detachable power transformer, suitable for short-time operation (transient use for 20 minutes daily, transient use for 30 minutes daily, or in clinic use for 60 minutes...
weekly), and not designed for use in the presence of flammable anaesthetic mixtures. The device contains no heating systems and the only intentionally emitted energy is near-infrared light.

**Medical Electrical and Product System Safety**

The Biolux LED device medical device has been designed to comply with the following harmonized standards:


The LED Array currently selected for the Biolux LED device has been classified by the manufacturer (according to IEC 60825-1) as a Class 1M device “Safe under reasonably foreseeable conditions”.

To assure patient safety against any possible thermal effects of the LED, an integral temperature sensor has been built into the Investigational Device headset. The system software will automatically shut down the Biolux LED device if the temperature sensor indicates 41°C or greater.

In order to minimize as much as possible any risks to the patient associated with the electrical system, the Controller unit and the LED Array have been powered at 24V DC using a medically approved power supply, which limits leakage currents to less than 10µA.

**Preliminary Risk Assessment**

A preliminary risk analysis has been carried out on the Biolux LED device investigational device in accordance with ISO 14971:2007 “Medical devices – Application of risk management to medical devices.”

After review of the risks associated with the use of the Biolux LED device prototype in the feasibility study, the residual risk is considered acceptable as none of the recognized hazards leads to a risk within the intolerable range. The ranking of each potential risk, after all
recommended actions and mitigations were taken, did not exceed RPN = 24, which is
considered to be an acceptable risk when weighed against the benefits of the products.

**Table 1 – Risk Level Table**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>RPN Range</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 to 25</td>
<td><strong>Negligible</strong> Risk – acceptable as implemented.</td>
</tr>
<tr>
<td>2</td>
<td>26 to 35</td>
<td><strong>Tolerable</strong> Risk – risk verified, validated and approved through review of the design to be as low as reasonably achievable (ALARA). Additional actions may need to be taken to reduce risk to a lower level.</td>
</tr>
<tr>
<td>3</td>
<td>36 to 125</td>
<td><strong>Intolerable</strong> Risk – unacceptable as is based on the pre-established criteria for risk acceptability; a reduction in occurrence is typically required.</td>
</tr>
</tbody>
</table>

Biolux concludes that the Biolux LED device prototype does not contain foreseeable risks of intolerable levels. The device is designed and manufactured such that, when used as intended, it will not compromise the conditions of safety of the patients and operator, and any remaining risk is managed with a high level of protection of health and safety.

Biolux LED Device User Guide for Patients

Manufacturer: Biolux Research Ltd.

INVESTIGATIONAL DEVICE

– TO BE USED UNDER THE SUPERVISION OF QUALIFIED INVESTIGATORS ONLY –

USE ONLY AS DIRECTED

Please read this manual in its entirety, before beginning treatment with the BIOLUX LED Device.

Before using the Biolux LED Investigational Device, ensure you have signed the Informed Consent document and have been thoroughly trained by your Orthodontist/Dentist on use of the Biolux LED Investigational Device.

The LED device emits an intense beam of invisible near-infrared light.

DO NOT STARE DIRECTLY AT THE LIGHT SOURCE.

Laser Radiation

Do Not View Directly with Optical Instruments

Class 1M Laser Product

Safe under reasonably foreseeable conditions

Classified per IEC 60825-1, Ed.2, 2007

WARNINGS:

• As with any electrical device, DO NOT use the Biolux LED device in or near water or heat producing appliances as they may damage the device and may pose possible fire hazards. Keep the Biolux LED device away from the reach of children.
• This device has not been tested in conjunction with High Frequency (HF) surgical
equipment (e.g., electrocautery) and should not be used with such equipment.

- Care should be exercised when handling the unit, to avoid damaging the Biolux LED device components. Extreme force should never be applied when setting up or storing the device.
- The device controller should be placed on a stable flat surface.
- The investigational unit should be used while sitting.
- Cables should be routed away from where people can trip on them, and kept away from pets and children.
- The device should be kept out of the reach of children.
- Do not cover the Array heat-sink vents.
- Do not use the investigational device if excessive heat is present.
- Use the appropriate laser safety glasses provided with the investigational device.
- The device is to be used when resting or performing passive activity such as listening to music or reading.
- The device should not be used by a photosensitive patient. A medical professional should be consulted if this skin irritation or burns occur or are suspected.
- Use should be discontinued if adverse reactions are noticed, in which case please inform your study dentist immediately.
- The device should not be used by a patient with epilepsy. A medical professional should be consulted if epilepsy is suspected.
- Do not use on patient with known acute infection.
- Use the investigational device as directed, treat gently, avoid mechanical mistreatment and do not use the device if damage is suspected.
- Do not open or tamper with the case. Servicing should be performed only by the manufacturer.

**CAUTION: Any changes or modifications to this equipment not expressly approved by the manufacturer will void the Qualified Investigator’s authority to operate and/or prescribe this equipment for use.**

**Safety Information: CAUTIONS**

- To ensure that the Treatment Array remains in the correct position, the patient should always keep their mouth closed and their teeth together during treatment.
• Prior to removing the Headset, turn off the Biolux LED device reducing the chance of shining the bright light directly in the patient’s eyes.

• The Treatment Array will be warm to touch during and after treatment, this is normal. If it becomes hot or uncomfortable to touch, discontinue treatment and contact your study dentist.

• The Treatment Array should not be covered. If it is covered, the Treatment Array could overheat. (An obstruction could be caused by an improperly positioned pillow or by long hair, for example).

• A small degree of tingling, warm feeling and pulsing is normal in the tissue and jaw during and after an LED device treatment session. Most patients find this comforting and soothing. If a patient experiences pain, discontinue the treatment.

• The Biolux LED device is programmed with self-diagnostic software that runs automatically at the beginning of every treatment session to verify that no system performance degradation has occurred. When the system detects a fault, the following warning message is displayed:

  “Fault detected – Return to Dentist”

• In the case of a fault, discontinue the use of the unit immediately. Please contact your study dentist for a replacement.

For instructions on correct assembly and use of the Biolux LED device, please read this guide in its entirety.

About the Biolux LED Device

The Biolux LED device is an extra-oral, light emitting diode (LED) photobiomodulation device intended for the stimulation and acceleration of OTM velocity. The device LED light with wavelengths in the near-infrared spectrums.

The Biolux LED device is an investigational device intended to be operated under dentist prescription and to be used by eligible patients in a home setting.

Before Using the Biolux LED device

Please check package contents to ensure that all parts are enclosed and in good condition.

Your Biolux LED device comes with the following components:
Your Biolux LED device treatment

Always operate the unit while seated in a comfortable position, with a table nearby for the controller. Make sure you are close to a household electrical outlet and that the power cords do not obstruct pathways. You should plan for uninterrupted time and remain still during your treatment. You may watch television, read, or listen to music if you wish. Before commencing treatment, ensure your hands are clean and dry. Do not adjust the Headset.

IMPORTANT: At any time you may stop treatment by pressing the on/off button at the top of the Controller, or by unplugging the Power Adaptor, or by unplugging the Treatment Array from Controller. To avoid looking into the bright light, do not remove the Headset until the power is off. If the Headset is removed during treatment, a safety mechanism places the Biolux LED device into standby mode, where the Treatment Array turns off automatically. Once the Headset is replaced the treatment will resume (provided the interval is less than 15 minutes).

1. Connect the Power Adaptor to the Controller and plug the Power Adaptor into the wall. The unit turns on automatically.

2. Place the Headset on with the nose and the earpieces firmly in contact with the bridge of the nose and the top of the ears. Make sure that the Headset fits as it did at the dental office and that it feels secure.

3. Plug the Treatment Array cable into the #1 socket on the bottom left of the Controller.

4. If two Treatment Arrays are to be used, plug the second Treatment Array cable into the #2 socket.

5. The screen should display the number of sessions left and a prompt to press ► to start.

If “No Prescriptions - Return to Dentist” appears on the screen, the unit has not been configured, and must be returned to the dentist for programming.

If “Treatments Completed - Return to Dentist” appears on the screen, treatment has been completed and the unit is to be returned to the dentist.

6. Press the ► Button to start the session.

During the treatment session, the Controller displays the remaining treatment time. Pause the treatment at any time by pressing the “►” button.

If the treatment session pauses, one of the following messages may appear on the
screen. Please follow the instructions.

“**Check Headset Connection.**” Please check that the plugs are connected to the correct sockets.

“**Temperature is ___ C Pausing to cool off!**” Once the Treatment Array has cooled, the session will resume automatically.

“**It seems that the Headset is not being worn. Please ensure it is correctly positioned**” Reposition the headset and session will resume automatically.

“**Headset position may be wrong. Check its position - or - press “►” to continue anyway**” Reposition headset and session will resume automatically - or - press “►” if you are sure the headset is positioned correctly.

Normally the treatment will continue automatically after a problem is corrected. If the pause is too long, this message will be seen:

“**Pause was too long. Please power-off and restart the session.**”

In this case, the session timer will begin again from the start.

7. Upon completion of the required treatment, the Controller will display a message that the session is complete. Press the power button at the top of the Controller to turn the unit off.

8. Remove the headset, and store all the Biolux LED device equipment in the protective carrying case. For convenience, keep all the cables connected between treatments. To reduce energy consumption when the Treatment Array is not in use, unplug the power adaptor from the wall socket.

9. Once all treatments have been completed, unplug all accessories, repack the Biolux LED device into the carrying case and return the Biolux LED device equipment to your dentist.

When unplugging cables, please remember to pull directly on the plug.

For more information or assistance with using the Biolux LED device, please consult your dentist.
A6. Participant Informed Consent Documentation

Patient Informed Consent Form

Project Title: The effect of light emitting diode (LED) phototherapy on OTM in humans.

Study Doctor: Dr. Sean Chung

Why are you being given this form?
You are being asked to participate in a research study while you are currently undergoing orthodontic treatment.
This study will evaluate the initial results of using a prototype medical device in accelerating tooth movement during orthodontic treatment. The light emitting diode (LED) device is a phototherapy device that LED light to produce therapeutic wavelengths in the near-infrared spectrums that are thought to stimulate bone cells to regenerate and heal faster. The Biolux LED device is an extraoral (outside of your mouth) device that the patients wear on their head for a period of time each day to receive treatment.

Figure 1: Biolux LED Device
This study and the use of the prototype Biolux LED device have received Investigational testing authorization from Health Canada. At this time the Biolux LED device is not available for use outside of research studies.

The information in this form is intended to help you understand exactly what we are asking of you, so that you can decide whether or not you want to participate in this study. Please read this consent form and the BIOLUX User Guide for Patients carefully and ask all the questions you might have before deciding whether or not to participate in this study. Your participation in this study is entirely voluntary and a decision not to participate will not in any way affect any future treatment.

Why is the study being done?

The purpose of the study is to evaluate the effectiveness of a LED phototherapy on the rate of OTM. The LED device is thought to provide light energy to bone tissue cells which absorb the light energy and convert to chemical energy. This energy is subsequently used in bone regeneration and growth. Traditional orthodontic treatment with appliances typically takes 12 to 36 months and LED phototherapy may shorten this treatment period, to the benefit of the patient. This study is intended to include that participation of approximately 40 patients in a University of Toronto Faculty of Dentistry Graduate Orthodontic clinic.

What will you be asked to do?

Your LED device will be programmed in accordance with the specific therapy that best applies to your condition. Subsequently, you will be shown how to wear the headset, how to connect the various components, and how to power on and off the device. More detailed information about the use of the LED device is contained in the BIOLUX User Guide for Patients document. Finally, your study orthodontist/dentist will define with you a schedule for your specific therapy program, including planned follow-up visits (typically at 2 six week internals), where the study orthodontist/dentist will take records to measure tooth positioning and also adjust the orthodontic appliances as per the regular planned orthodontic treatment. Each visit to the study orthodontist/dentist is typically 1 hour long. The entire study duration is expected to be 90 days.

Treatment with the LED device will be carried out on one quadrant of your mouth, while the
contralateral (opposite) side will not be treated and serve as control for comparison purpose. If after 90 days of treatment the study orthodontist/dentist deems it desirable, treatment with the LED device on the contralateral (opposite) side may occur for a further 90 days to balance the bilateral mechanics.

**IT IS CRITICAL FOR THE OUTCOME OF THIS STUDY AND YOUR OWN SAFETY THAT**

**YOU ADHERE TO THE TREATMENT SCHEDULE THAT YOUR STUDY ORTHODONTIST/DENTIST HAS IDENTIFIED FOR YOU.**

**Potential harms / risks / benefits**

Although this LED therapy has been researched in the medical literature with respect to healing wounds, increased blood circulation and stimulation of soft tissue and bone growth, the Biolux LED device is an experimental device that has not yet been approved by Health Canada for use outside of research studies like this one. Some known limited risks, although rare, are associated with placing the LED source on the surface of the skin.

These risks and discomforts may include:

- Skin allergic reaction (such as hives, swelling of the face, lips, tongue and/or throat which may cause difficulty in breathing or swallowing and, if not treated promptly, could become life-threatening) due to contact with the device or its components. The types of plastic materials that may come into contact with the skin include polyurethane, polycarbonate, neoprene, nylon and styrene-butadiene. No latex is included in the Biolux LED device.

- If you are, or will be, using any medication, herbal or “natural” remedy, during the course of this study, please inform your study orthodontist/dentist immediately. Please check
with the study orthodontist/dentist before you begin taking a new medication while in this study.

• LED light exposure to the eye (if the Face Frame is not properly worn during the treatment). Do not stare directly at the light, and close your eyes when taking the headset on and off.

As with any clinical test procedure, there may be additional unforeseen risks involved in taking part in this study. Although very unlikely, if you suffer a serious or lasting injury as a result of participation in this study, it may affect your ability to obtain private health insurance, your employability, and/or quality of life.

If significant new findings, which may be related to your willingness to continue to participate in this study, become known while this study is underway, you will be informed as soon as possible. If you experience any adverse reaction (unwanted effect or health problem) or notice any unusual sign or symptom, you must contact your study orthodontist/dentist immediately.

If you are a woman able to become pregnant, there might be risks to the embryo or fetus which are currently unforeseeable.

You may not benefit directly from your participation in this study. Although the treatment period may be shortened, this is not guaranteed. You will not benefit financially from any commercial gains from sales of any product resulting from this study.

Commercialization
Research carried out on the results of this study may lead to the development of marketable procedures or devices and any benefit from the commercial products will remain with the manufacturer.

**Alternatives to participating in the project**

You may choose not to participate in the study and still receive regular orthodontic treatment.

**Privacy and confidentiality**

Dental and medical records that contain your identity will be treated as confidential in accordance with the *Canadian Personal Information Protection and Electronic Document Act* and provincial privacy laws. Your identity will be kept confidential at all times, except where disclosure is required by law.

As part of this research, the study doctor will collect the results of your study-related procedures and may also access your personal medical records for health information such as past medical history and test results. Information from this study may also be submitted to the sponsor, Biolux Research Ltd., and to Health Canada. Information collected from the study site will not contain your name. Your dental/orthodontic records, which include your name, may be inspected at the study site by the monitor(s), auditor(s), representatives of the Manufacturer and research ethics committees (an independent committee that reviewed the ethical aspects of this study to help protect the rights and welfare of study participants). This inspection is to verify the accuracy of study records and of the clinical trial procedures and/or data without violating your confidentiality and to the extent permitted by the applicable laws and regulations. This
information may also be reported to Health Canada in the case of adverse events observed in the course of the research. If the results of the study are published, your identity will remain confidential. Data resulting from this study shall be retained at University of Toronto in controlled electronic and hardcopy records. You have the right to check your study records and request changes if the information is not correct.

While every effort will be made to protect the privacy of your information, absolute confidentiality cannot be guaranteed. However, this does not limit the duty of the researchers and others to protect your privacy.

By signing this *Patient Information and Consent Form*, you consent to the collection, access, use and disclosure of your information as described above.

**Compensation for injury and legal rights**

By signing this consent form you are not waiving your legal rights, nor releasing the study orthodontist/dentist or manufacturers of the device from their legal and professional obligations.

**Reimbursement for expenses and costs of participating**

There will be no cost to you, your private medical insurance (if any), or the public health insurance plan, for the use of the study device in addition to what normally charged by your dentist for the same orthodontic work. You will not be paid for your participation in this study, nor will you be reimbursed for any additional expenses, related to your participation in this study, that you may incur.

**You have the right to change your mind**
Your participation is entirely voluntary. You can refuse to take part in this project at this point or withdraw from it at any time during the study, without incurring any penalty or loss of benefits to which you are otherwise entitled. If you decide to withdraw during the course of the study, any clinical information collected from you until then may still be used for the purpose of the study. The study orthodontist/dentist may also withdraw you from the study if you do not follow the instructions you received from the study personnel, if the study orthodontist/dentist feels it is in your best interests to be withdrawn, if the study sponsor discontinues the study, or for administrative reasons. You may be withdrawn without your consent, but the study orthodontist/dentist will explain to you why.

Who to contact if you have any further concerns or questions?

Any further questions or concerns may be directed to Dr. Sean Chung.

(416) 979-4912 x 2.

In case of an emergency, please contact Dr. Sean Chung at the above phone number, OR go to the nearest hospital emergency department.

Ethics review

Please contact Dr. Sean Chung, if you:

• have questions about your role and rights as a research participant

• wish to obtain more information about clinical research in general

• have concerns, complaints or general questions about the research, or

• wish to provide input about the research study
Statement of Patient Consent

I, ________________________________, have been given enough time and opportunity to read and understand the information in this informed consent and ample time and opportunity to ask questions. All my questions have been answered to my satisfaction. I have had sufficient time to consider whether to participate in this study. I understand that my participation in this study is entirely voluntary and that I may withdraw from the study at any time without penalty.

I understand that the study device is for my exclusive use only. I will not share it with anyone and will store it in a safe place away from children or others for whom it is not intended.

The study orthodontist/dentist has my permission to tell my regular doctor about my being in this study:

YES   NO

I voluntarily consent to participate in this study and will be given a signed copy of this form to take home with me.

Subject’s Signature ____________________________  Date___________________

(Please also initial each page of this Informed Consent Form)

Statement of Person Obtaining Consent:

To the best of my knowledge, the information that I, ______________________________
have provided in the response to any questions from the subject, fairly represents the study.

I will ensure that the subject receives a copy of this consent form.

Person Obtaining Consent’s Signature __________________________ Date____________________

Subject’s Initials __________

**Statement of Study Investigator**

(Investigator preferably to sign the consent form on the same date as the subject, but prior to
first patient visit)

I acknowledge my responsibility for the care and well being of the above subject, to respect the
rights and wishes of the subject, and to conduct the study in compliance with all the ethical
standards that apply to research studies that involve human subjects and with applicable Good
Clinical Practice guidelines and regulations.

Investigator Name (printed) __________________________

Investigator’s Signature ___________________________ Date____________________
A7. Research Contribution Agreement between the University of Toronto and BIOLUX Research Ltd., the Manufacturer of the Device.

RESEARCH CONTRIBUTION AGREEMENT

This agreement (the “Agreement”) is made in two original counterparts effective December 16, 2011 (the “Effective Date”).

BETWEEN:

THE GOVERNING COUNCIL OF THE UNIVERSITY OF TORONTO
(the “University”)

- and -

BIOLUX RESEARCH LTD
825 Powell Street
Suite 220
Vancouver, British Columbia V6A 1H7
(“Biolux”)

WHEREAS, the University is conducting a research project entitled “The Effect of Light Emitting Diode (LED) Phototherapy on Orthodontic Tooth Movement in Humans” (the “Project”) under the supervision and direction of Drs. Bryan Tompson and Siew-Ging Gong of the University’s Faculty of Dentistry (the “Principal Investigators”);

AND WHEREAS, the University requires light emitting diode phototherapy devices for use on the Project;

AND WHEREAS, Biolux has invented and is the Canadian distributor of a device called the OrthoPulse® for delivery of light emitting diode treatment for bone regeneration and is willing to support the Project by contributing the OrthoPulse® devices (the “Devices”) needed for the conduct of the Project;

NOW, THEREFORE, the parties agree as follows:

1.0 THE PROJECT

1.1 Project. The University will perform the Project as described in the attached Appendix “A” under the supervision and direction of the Principal Investigators, together with such additional personnel as the University may assign.

1.2 Contribution. Biolux will provide at no cost to the University, the Devices needed for performance of the Project, including shipping and handling, as further described in Appendix “B”.

1.3 Confidential Information. If either party discloses confidential information to the other party under this Agreement, the disclosing party will identify such information as “confidential” in writing at the time of its transmittal, or so reduced to writing within ten (10) days thereafter (“Confidential Information”). The receiving party will safeguard and not disclose such Confidential Information to third parties for a period of five (5) years of receipt from the disclosing party. Confidential Information will not include information that:
Research Contribution Agreement between: The Governing Council of the University of Toronto and Biolux Research Ltd
Project entitled: "The Effect of Light Emitting Diode (LED) Phototherapy on Orthodontic Tooth Movement in Humans"

Effective Date: December 15/2011

(a) the receiving party can demonstrate through documentary records to have been known to the receiving party prior to its receipt from the disclosing party;
(b) is or becomes publicly available other than through an act or omission of the receiving party or any of its employees;
(c) the receiving party lawfully obtained from sources under no obligation of confidentiality;
(d) is required to be disclosed under the requirement of judicial process, regulatory authority or law, and the receiving party has given thirty (30) days advance notice to the disclosing party.

Notwithstanding anything contained herein, each party may disclose Confidential Information to its officers, employees, consultants, agents, and students on a need-to-know basis in relation to the Project, provided that such persons agree to be bound by terms at least as restrictive as those contained herein.

2.0 RESEARCH RESULTS

2.1 Ownership. The University shall own all intellectual property, including without limitation, all research results, technical information, data, know-how, models, drawings, specifications, prototypes, inventions, whether or not patentable, software, copyrights, and other intellectual property that is discovered, created or reduced to practice in performance of the Project ("Intellectual Property"). The University may assign its interest in Intellectual Property according to the University's applicable policies and procedures.

2.2 Dissemination. The University reserves on behalf of itself, and the Principal Investigators, the right to disseminate information or otherwise publish the Project results without restriction. Biolux's support of the Project shall be acknowledged in all such publications.

2.3 Results. The University will provide Biolux with a copy of the results of the Project for review and comment prior to publication. The University will consider any comments received from Biolux within thirty (30) days of submission of such information to Biolux, but is not obligated to incorporate such comments into its publication(s). All such information provided to Biolux shall be considered University's Confidential Information.

2.4 Similar Research. Nothing in this Agreement will be construed to limit the freedom of the University or of its researchers from engaging in similar research under agreements with parties other than Biolux.

3.0 TERM AND TERMINATION

3.1 Term. This Agreement shall enter into force as of the Effective Date and shall terminate on December 31, 2014, unless terminated earlier in accordance with Section 3.2.

3.2 Termination. The University may terminate this Agreement upon sixty (60) days written notice to the Sponsor. The Agreement may also be terminated by mutual written agreement of the parties.

3.3 Effect of Termination. The following provisions shall survive termination or expiration of this Agreement: Sections 1.3, 2.1, 2.2, 3.3, 4.1, 4.2 and 4.3 in accordance with their terms, together with any provisions necessary to interpret or give effect to the foregoing sections.
4.0 MISCELLANEOUS

4.1 Disclaimer. The University makes no warranties or representations regarding its ability to achieve, nor shall it be bound to accomplish, any particular objective or results from the Project. The University shall have no liability whatsoever to Biolux in connection with the Devices, including damage to the Devices however caused, or any Project results described in any report or other information that may be provided to Biolux.

4.2 Limitation of Liability. The University will indemnify and save harmless Biolux against all costs, suits or claims on account of injuries (including death) to persons participating in the Project caused by the wilful misconduct or negligent act or omission of personnel of University during the performance of this Agreement. Biolux will indemnify and save harmless the University and its employees, students and agents against all costs, suits or claims resulting from: (i) the University’s use of the Devices unless caused by the wilful misconduct or negligent act or omission of personnel of the University, (ii) any third party claims of infringement of any copyright or patent related to the University’s use of the Devices or, (iii) the use by Biolux or its affiliates, its customers or licensees of any information or intellectual property developed under this Agreement.

4.3 Use of Names. Neither party shall use the name of the other party, or of any member of the other party’s personnel, in any advertising or publicity without the prior written approval of the other party’s authorized representative. However, both parties may make the following information a matter of public record: names of Principal Investigators; Principal Investigators’ department; University’s name; Biolux’s name; title of the Project; duration of the Project; and contribution provided.

4.4 Notices. Notices under this Agreement shall be sent to the parties as follows or to such other person as a party may designate in writing:

(a) to the University:

i. to the Principal Investigator (for technical and scientific matters):

Dr. Bryan Tompson
University of Toronto
Faculty of Dentistry
124 Edward Street
Toronto, ON M5G 1G6
Tel: 416-979-4900 ext. 4605
Fax: 416-979-4396
Email: bryan.tompson@dentistry.utoronto.ca

ii. for legal and administrative matters:

Jennifer Fraser
Director
Business Development and Commercialization - Life Sciences
University of Toronto
Innovations & Partnerships Office
Banting Institute
100 College Street, Suite 413
Toronto, ON M5G 1L3
Tel: 416-946-5515
Fax: 416-978-6052
Email: jen.fraser@utoronto.ca
4.5 Independent Parties. The parties are independent parties and nothing in this Agreement shall constitute either party as the employer, principal or partner of or joint venturer with the other party. Neither party has any authority to assume or create any obligation or liability, either express or implied, on behalf of the other party.

4.6 No Assignment. Except as permitted by Section 2.1, neither party may sell, assign, encumber, licence or otherwise transfer any of its rights, duties or obligations under this Agreement without the prior written consent of the other party, which consent may not be unreasonably withheld.

4.7 Successors. This Agreement binds and enures to the benefit of the parties hereto and their respective heirs, successors and permitted assigns.

4.8 Interpretation. This Agreement shall be governed by and construed in accordance with the laws of the Province of Ontario in Canada. In the event that a court of competent jurisdiction holds any provision of this Agreement to be invalid, such holding shall have no effect on the remaining provisions of this Agreement, which shall continue in full force and effect. Headings are used for convenience only and shall not be used to interpret the provisions of this Agreement.

4.9 Entire Agreement. This Agreement is the entire agreement of the parties with respect to its subject matter and no change or modification shall be valid unless it is in writing and signed by both parties.

IN WITNESS WHEREOF by signature of their respective authorized officers, the parties agree to be bound by the terms of this Agreement.

THE GOVERNING COUNCIL OF
THE UNIVERSITY OF TORONTO

Name: Jennifer Fraser
Title: Director, Business Development and Commercialization - Life Sciences
Date

BIOLUX RESEARCH LTD

Name: KEVIN STRANGE
Title: President & CEO
Date Dec-16/2011
APPENDIX “A”

Description of the Research

Project Title

The Effect of Light Emitting Diode (LED) Phototherapy on Orthodontic Tooth Movement in Humans

Research Team

Dr. Bryan Tompson  
Dr. Siew-Ging Gong  
Dr. Scan Chung

Description

Orthodontic treatment is associated with an increased risk of caries, periodontal disease and root resorption. Improvements in treatment efficiency leading to shorter treatment duration can help alleviate these challenges. This study will lay a foundation for light emitting diode (LED) phototherapy mediated increases in orthodontic tooth movement (OTM). Specifically, this study will utilize a split-mouth design to investigate the role of LED phototherapy in influencing the amount/rate of orthodontic tooth movement during the first 3 months of orthodontic space closure in cases requiring bilaterally symmetric extractions.
Research Contribution Agreement between: The Governing Council of the University of Toronto and Biolux Research Ltd
Project entitled: "The Effect of Light Emitting Diode (LED) Phototherapy on Orthodontic Tooth Movement in Humans"

Effective Date: December 16/2011

APPENDIX “B”

Device Arrangements

Device

OrthoPulse® devices sufficient for the conduct of the Project will be contributed by Biolux, including all shipping and handling costs, at no cost to the University of Toronto.

Quantity Required

During the course of the Project, the University and Biolux will discuss and confirm the quantity, timing and other arrangements for provision of the Devices as needed.

Disposition at end of Project

On completion of the Project, Biolux will provide the University with retention, return or disposal instructions for the Devices. Any associated shipping, handling or disposal costs will be borne by Biolux.

Coordination

Dr. Sean Chung will be the University of Toronto contact for coordination of this activity.
APPENDIX B: Statistical Test Results.

B1. A repeated measures comparison of the rates of extraction space closure with OTM.

Solution for Fixed Effects

Standard

| Effect      | group | Estimate | Error  | DF  | t Value | Pr > |t| |
|-------------|-------|----------|--------|-----|---------|-------|----|
| Intercept   | 0     | 0.05617  | 0.008599 | 51.7| 6.53    | <.0001|
| group 1     | -0.01235 | 0.01147  | 39.9   | -1.08| 0.2882  |
| group 2     | 0     | .        | .      | .   | .       | .     |
| days        | -0.00026 | 0.000142 | 44.3   | -1.85| 0.0706  |
| days*group 1| 0.000272 | 0.000193 | 39.9   | 1.41 | 0.1677  |
| days*group 2| 0     | .        | .      | .   | .       | .     |

Type 3 Tests of Fixed Effects

Num Den

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<td>39.9</td>
<td>1.16</td>
<td>0.2882</td>
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<tr>
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<td>39.9</td>
<td>1.97</td>
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B2. A repeated measures comparison of the change in extraction space size over time associated with tooth movement: Linear Model.

### Solution for Fixed Effects

| Effect   | group | Estimate | Standard Error | DF  | t Value | Pr > |t| |
|----------|-------|----------|----------------|-----|---------|-------|
| group    | 1     | 5.2270   | 0.5356         | 22.4| 9.76    | <.0001|
| group    | 2     | 5.0036   | 0.5356         | 22.4| 9.34    | <.0001|
| days*group | 1   | -0.04151 | 0.002827       | 58.7| -14.69  | <.0001|
| days*group | 2   | -0.03884 | 0.002827       | 58.7| -13.74  | <.0001|

### Type 3 Tests of Fixed Effects

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<tr>
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<td>59.1</td>
<td>0.45</td>
<td><strong>0.5066</strong></td>
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</table>
B3. A repeated measures comparison of the change in extraction space size over time with tooth movement: Quadratic Model.

Solution for Fixed Effects

Standard

| Effect  | group | Estimate | Error   | DF  | t Value | Pr > |t| |
|---------|-------|----------|---------|-----|---------|-------|
| Intercept |       | 5.0681   | 0.5347  | 22.9 |  9.48   | <.0001 |
| group   | 1     | 0.1965   | 0.4221  | 21  |  0.47   | 0.6463 |
| group   | 2     | 0        | .       | .   | .       | .     |
| days    |       | -0.04891 | 0.008006| 57.2 | -6.11   | <.0001 |
| days*group | 1     | -0.00548 | 0.006996| 59.1 | -0.78   | 0.4362 |
| days*group | 2     | 0        | .       | .   | .       | .     |
| days*days |      | 0.000132 | 0.000098| 57.4 |  1.34   | 0.1842 |
| dayslight |      | 0.006279 | 0.01277 | 59.4 |  0.49   | 0.6248 |

Type 3 Tests of Fixed Effects

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<td>59.4</td>
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B4. A repeated measures comparison of the change in extraction space size over time with OTM, adjusted for cumulative LED received - Linear Model.

Solution for Fixed Effects

| Effect    | group | Estimate | Error | DF   | t Value | Pr > |t| |
|-----------|-------|----------|-------|------|---------|------|---|
| Intercept |       | 5.0035   | 0.5349| 22.4 | 9.35    | <.0001|
| group     | 1     | 0.2130   | 0.4186| 20.2 | 0.51    | 0.6164|
| group     | 2     | 0        | .     | .    | .       | .    |
| days      |       | -0.03844 | 0.002803| 57.9 | -13.86  | <.0001|
| days*group| 1     | 0.01638  | 0.01416| 64.7 | 1.16    | 0.2515|
| days*group| 2     | 0        | .     | .    | .       | .    |
| Cum_LED   |       | -0.02361 | 0.01684| 65.1 | -1.40   | 0.1657|

Type 3 Tests of Fixed Effects

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<td>Cum_LED</td>
<td>1</td>
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</table>
B5. Differences of least squares comparison for the change in extraction space size over time with OTM as a function of cumulative LED received, at Days 20, 45, 60 and 80.

Differences of Least Squares Means

Standard

| Effect | group | group | days | Cum_LED | Estimate | Error | DF  | t Value | Pr > |t| | Adjustment |
|--------|-------|-------|------|---------|----------|-------|-----|---------|-------|-----|----------------|
|        | 1     | 2     | 20.00|         | 0.5679   | 0.4787 | 30.9| 1.19    | 0.2445 | Tukey-Kramer |
|        | 1     | 2     | 45.00|         | 1.0124   | 0.7214 | 66.7| 1.40    | 0.1652 | Tukey-Kramer |
|        | 1     | 2     | 60.00|         | 1.2790   | 0.9025 | 72.8| 1.42    | 0.1607 | Tukey-Kramer |
|        | 1     | 2     | 80.00|         | 1.6346   | 1.1601 | 72.2| 1.41    | 0.1631 | Tukey-Kramer |

The Mixed Procedure

Differences of Least Squares Means

Adj Adj

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<tr>
<th>Effect</th>
<th>group</th>
<th>group</th>
<th>Adj P</th>
<th>Alpha</th>
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<th>Upper</th>
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</table>
### B6. A repeated measures comparison of the change in extraction space size over time with OTM, adjusted for sex - Linear Model

Solution for Fixed Effects

#### Standard

| Effect   | group | Sex1f | Estimate | Error | DF  | t Value | Pr > |t| |
|----------|-------|-------|----------|-------|-----|---------|-------|---|
| Intercept|       |       | 6.2216   | 0.7900| 17.2| 7.88    | <.0001|
| group    | 1     |       | 0.1316   | 0.3942| 16.3| 0.33    | 0.7427|
| group    | 2     |       | 0        | .     | .   | .       | .     |   |
| days     |       |       | -0.04022 | 0.001993| 59.4| -20.18  | <.0001|
| Sex1f    | 1     |       | -1.8102  | 0.9464| 14.9| -1.91   | 0.0752|
| Sex1f    | 2     |       | 0        | .     | .   | .       | .     |   |

#### Type 3 Tests of Fixed Effects

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<td>3.66</td>
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B7. A Repeated measures comparison of the change in extraction space size over time with OTM, adjusted for wire size – Linear Model.

Solution for Fixed Effects

| Effect   | group | 217 | Estimate | Error | DF       | t Value | Pr > |t| |
|----------|-------|-----|----------|-------|----------|---------|-------|---|
| Intercept|       |     | 3.2486   | 0.9188| 16.6     | 3.54    | 0.0026|
| group    | 1     |     | 0.1316   | 0.3942| 16.3     | 0.33    | 0.7427|
| group    | 2     |     | 0        | .     | .        | .       | .     |   |
| days     |       |     | -0.04023 | 0.001993| 59.3 | -20.18 | <.0001|

Wiresize116_217

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<th>Estimate</th>
<th>Error</th>
<th>DF</th>
<th>t Value</th>
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Wiresize116_217

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<th>Error</th>
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Type 3 Tests of Fixed Effects

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<tbody>
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<td>days</td>
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</table>
B8. Pre-study sample size calculations

Comparison of 2 rates: taken from Youssef et al., 2008

Equation: \[ \frac{(U+V)^2(u1+u0)}{(u1-u0)^2} \]

U (for 80% power) = 0.84           V (for 5% significance) = 1.96

u1, u0 = rates of tooth movement

\[ u1=2.027+/-0.14\text{mm/month} \quad u0=1.109+/-0.11\text{mm/month} \]

\[ \sqrt{(1.96+0.84)^2(2.027+1.109)} / (2.027+1.109)^2 = 29.174 \sim 30 \text{ patients} \]

Comparison of 2 means: taken from Cruz et al., 2008

Equation: \[ \frac{(U+V)^2(\sigma1^2 + \sigma2^2)}{(u1-u0)^2} \]

U (for 80% power) = 0.84           V (for 5% significance) = 1.96

u1, u2 = means of tooth movement

\[ u1=4.39\text{mm} \quad u2=3.1\text{mm} \]

\[ \sigma1, \sigma2 = \text{standard deviation taken from Cruz et al., 2008} \quad \sigma1=0.27 \quad \sigma2=0.24 \]

\[ \sqrt{(1.96+0.84)^2(0.27^2+0.24^2)} / (4.39-3.1)^2 = 0.96 \sim 1 \text{ patient} \]

Comparison of 2 means: taken from da Silva Sousa et al., 2009

Equation: \[ \frac{(U+V)^2(\sigma1^2 + \sigma2^2)}{(u1-u0)^2} \]

U (for 80% power) = 0.84           V (for 5% significance) = 1.96

u1, u2 = means of tooth movement

\[ u1=3.09\text{mm} \quad u2=1.6\text{mm} \]

\[ \sigma1, \sigma2 = \text{standard deviation taken from da Silva Sousa et al., 2009} \quad \sigma1=1.06 \quad \sigma2=0.63 \]

\[ \sqrt{(1.96+0.84)^2(1.06^2+0.63^2)} / (3.09-1.6)^2 = 5.369 \sim 6 \text{ patients} \]
B9. Post-Study Power Analyses

Two-Sample Power Analysis on actual rates seen in this study

Numeric Results for Two-Sample T-Test

Null Hypothesis: Mean1=Mean2. Alternative Hypothesis: Mean1<>Mean2

The standard deviations were assumed to be unknown and unequal.

<table>
<thead>
<tr>
<th>Power</th>
<th>N1</th>
<th>N2</th>
<th>Ratio</th>
<th>Alpha</th>
<th>Beta</th>
<th>Mean1</th>
<th>Mean2</th>
<th>S1</th>
<th>S2</th>
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</thead>
<tbody>
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<td>17</td>
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<td>0.040</td>
<td>0.039</td>
<td>0.002</td>
<td>0.002</td>
</tr>
</tbody>
</table>

References


Report Definitions

Power is the probability of rejecting a false null hypothesis. Power should be close to one.

N1 and N2 are the number of items sampled from each population. To conserve resources, they should be small.

Alpha is the probability of rejecting a true null hypothesis. It should be small.

Beta is the probability of accepting a false null hypothesis. It should be small.

Mean1 is the mean of populations 1 and 2 under the null hypothesis of equality.

Mean2 is the mean of population 2 under the alternative hypothesis. The mean of population 1 is unchanged.
S1 and S2 are the population standard deviations. They represent the variability in the populations.

**Summary Statements**

Group sample sizes of 17 and 17 achieve 29% power to detect a difference of 0.001 between the null hypothesis that both group means are 0.040 and the alternative hypothesis that the mean of group 2 is 0.039 with estimated group standard deviations of 0.002 and 0.002 and with a significance level (alpha) of 0.05000 using a two-sided two-sample t-test.

**Two-Sample  Power Analysis**

**Numeric Results for 2-sample t-Test (Normal Distribution)**

(assuming a difference of 1 mm is Clinically different) With different hypothetical standard deviations

Null Hypothesis: Mean1=Mean2. Alternative Hypothesis: Mean1<>Mean2

The standard deviations were assumed to be unknown and unequal.

| Allocation |
|---|---|---|---|---|---|---|---|---|
| Power | N1 | N2 | Ratio | Alpha | Beta | Mean1 | Mean2 | S1 |
| 0.81477 | 24 | 24 | 1.000 | 0.05000 | 0.18523 | 1.950 | 2.950 | 0.500 |
| 0.81036 | 38 | 38 | 1.000 | 0.05000 | 0.18964 | 1.950 | 2.950 | 0.500 |
| 0.80585 | 29 | 29 | 1.000 | 0.05000 | 0.19415 | 1.950 | 2.950 | 1.000 |
| 0.80436 | 43 | 43 | 1.000 | 0.05000 | 0.19564 | 1.950 | 2.950 | 1.000 |
| 0.80715 | 54 | 54 | 1.000 | 0.05000 | 0.19285 | 1.950 | 2.950 | 2.000 |
| 0.80155 | 68 | 68 | 1.000 | 0.05000 | 0.19845 | 1.950 | 2.950 | 2.000 |
References


Report Definitions

Power is the probability of rejecting a false null hypothesis. Power should be close to one.

N1 and N2 are the number of items sampled from each population. To conserve resources, they should be small.

Alpha is the probability of rejecting a true null hypothesis. It should be small.

Beta is the probability of accepting a false null hypothesis. It should be small.

Mean1 is the mean of populations 1 and 2 under the null hypothesis of equality.

Mean2 is the mean of population 2 under the alternative hypothesis. The mean of population 1 is unchanged.

S1 and S2 are the population standard deviations. They represent the variability in the populations.

Summary Statements for different scenarios

Group sample sizes of 24 per group achieve 81% power to detect a difference of -1.000 between the null hypothesis that both group means are 1.950 and the alternative hypothesis that the mean of group 2 is 2.950 with estimated group standard deviations of 0.500 and 1.500 and with a significance level (alpha) of 0.05 assuming the actual distribution is normal.
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