Oral health-related quality of life in children and adolescents with Osteogenesis Imperfecta

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DEDICATION

I dedicate this thesis to my parents, Mohammadali and Azam, and my sister Zahra, who offered unconditional love and support and have always been there for me.

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LIST OF ABBREVIATIONS

Adjusted-DFT	Decayed /Filled Teeth adjusted for the number of teeth
COHRQoL	Children Oral Health Related Quality of Life
DFT	Decayed /Filled Teeth
DI	Dentinogenesis Imperfecta
DMFT	Decayed/Missing/Filled Teeth
EWB	Emotional well-being
FL	Functional limitation
HRQoL	Health Related Quality of Life
OHI-S	Simplified Oral Hygiene Index
OHRQoL	Oral Health Related Quality of Life
OI	Osteogenesis Imperfecta
OS	Oral symptom
QoL	Quality of Life
SWB	Social well-being

Abstract

Children and teenagers with Osteogenesis Imperfecta (OI), may have their Oral Health-Related Quality of Life (OHRQoL) affected by the oral traits of the disease. However, there is little that we know of OHRQoL and its determinants amongst this population. The aim of this thesis is to investigate the extent of associations between disease-related oral conditions and OHRQoL in children and adolescents having OI.

Aim: To estimate the extent of association between oral traits of OI and OHRQoL amongst children and adolescents suffering from OI.

Methodology: Children and adolescents aged 8-14 years were recruited in the context of a multicenter longitudinal study (Brittle Bone Disease Consortium) that enrolls individuals with OI in 10 centers across North America. Data on socio-demographic factors, and medical history were collected using a questionnaire. OHRQoL was assessed using the Child Perceptions Questionnaire (CPQ) versions for 8 to 10-year-olds (CPQ_{8-10}) and for 11 to 14-year-olds (CPQ_{11-14}). A comprehensive oral evaluation was performed at each center by calibrated dentists. A multivariate ordinal logistic regression was employed to adjust for the potential confounders.

Results: A total of 138 children and adolescents (62% girls) diagnosed with OI types I, III, IV, V and VI (n=65, 30, 37, 4 and 2, respectively) participated in the study. Caries experience (adjusted-DFT) and oral hygiene (OHI-S) were not statistically significantly different between OI types both in children and adolescents. Amongst all participants 34% (n=47) had dentinogenesis imperfecta (DI), 50% (n=69) had class III dental malocclusion, 36% (n=50) had posterior cross-bite and 28%

(n=39) had lateral open-bite. The prevalence of aforementioned traits are predominantly higher amongst patients having OI type III.

The only statistically significant determinants of negative impact on oral health-related quality of life was posterior cross-bite in the adolescent group with having the strongest association with functional limitation domain. Having posterior crossbite increases the odds of having higher grades of functional limitations by a factor of 6.1 (95% CI: 1.7- 22.6). Accordingly, having posterior crossbite increases the odds of having lower OHRQoL by 5.9 (95% CI: 1.6- 20.9) times amongst adolescents. No statistically significant association was observed in the children's group.

Conclusion: Regardless of OI type, teenagers with posterior cross bite experience significantly lower OHRQoL than those without.

Resume

Les enfants et les adolescents atteints d'ostéogenèse imparfaite (OI) peuvent avoir leur Santé bucco-dentaire Liée à la Qualité de Vie (QVLSD) affectée par les caractéristiques orales de la maladie. Cependant, nous connaissons peu de QVLSD et ses déterminants parmi cette population. L'objectif de cette thèse est d'examiner l'étendue des associations entre les conditions bucco-dentaires liées à la maladie et QVLSD chez les enfants et les adolescents qui souffrent d'OI.

Objectif : Estimer l'étendue de l'association entre les traits oraux de l'OI et de l'QVLSD parmi les enfants et les adolescents qui souffre d'OI.

Méthodologie : Des enfants et des adolescents âgés de 8 à 14 ans ont été recrutés dans le cadre d'une étude longitudinale multicentrique (Brittle Bone Disease Consortium) qui recrute des personnes atteintes d'IO dans 10 centres en Amérique du Nord. Les données sur les facteurs sociodémographiques et les antécédents médicaux ont été recueillies à l'aide d'un questionnaire. QVLSD a été évalué en utilisant des versions du Questionnaire sur la perception de l'enfant (CPQ) pour les 8 à 10 ans (CPQ8-10) et pour les 11 à 14 ans (CPQ11-14). Une évaluation orale complète a été effectuée dans chaque centre par des dentistes calibrés. La régression logistique ordinale multivariée a été utilisée pour ajuster les variables confondantes potentielles.

Résultats : Un total de 138 enfants et adolescents (62 % de filles) ayant reçu un diagnostic de type OI I, III, IV, V et VI (n = 65, 30, 37, 4 et 2, respectivement) ont participé à l'étude. La présence des caries (DFT ajustée) et l'hygiène buccale (OHI-S) n'étaient pas statistiquement significativement différentes entre les types d'OI chez les enfants et les adolescents. Parmi tous les participants, 34 % (n = 47) avaient une dentinogenèse imparfaite (DI), 50 % (n = 69) souffraient d'une malocclusion dentaire de classe III, 36 % (n = 50) enduraient une occlusion croisée

postérieure et 28 % (n = 39) avaient une béance latérale. La fréquence des traits susmentionnés est principalement élevée chez les patients atteint de l'OI de type III.

Le seul déterminant statistiquement significatif de l'impact négatif sur la qualité de vie liée à la santé bucco-dentaire était l'occlusion croisée postérieure dans le groupe des adolescents qui avait une forte association avec le domaine de la limitation fonctionnelle. Ayant l'occlusion croisée postérieure, augmente les chances d'avoir des grades supérieurs de limitations fonctionnelles par un facteur de 6,1 (95 % CI : 1,7 — 22,6). Par conséquent, le fait d'avoir une occlusion croisée postérieure augmente les chances d'avoir une QVLSD inférieure par un facteur de 5,9 (IC à 95 % : 1,6 à 20,9) chez les adolescents.

Aucune association statistiquement significative n'a été observée parmi le groupe des enfants.

Conclusion : Indépendamment du type de OI, les adolescents avec une occlusion croisée postérieure ont des QVLSD significativement plus faibles que les autres.

1. Introduction

Osteogenesis Imperfecta (OI) is a rare hereditary genetic disorder of increased bone fragility. Patients with OI can be clinically identified by fragile bones, recurrent fractures following by other abnormalities such as short stature, dentinogenesis imperfecta, blue sclera, scoliosis (spinal curvature), hearing loss, and pulmonary function deficiency (1-3).

OI patients of all ages experience a lower HRQoL (health-related quality of life) compared to healthy peers due to the traits of the disease which can result in pain, fatigue, and varying degrees of physical limitations. However, they have shown no significant difference in the psychosocial aspects of QoL when compared with a healthy population. (4-6). Also, patients of all ages with mild OI (type I) have rated their physical aspects of QoL better than those with severe OI (type III) (4-6). Children and teenagers with OI experience a lower quality of life than adults since they are more active and their bones are still growing, they are more susceptible to acute fracture pain, and they suffer from chronic pain caused by the skeletal malformation (7).

General health gets affected by oral health alterations through generating pain, changing what individuals eat and how they grow, look, speak, chew, taste food, socialize, enjoy life, and their feeling of social well-being (8, 9). The pathological effects of OI on dental tissues and the oral cavity usually develop in early childhood and during adolescence which may influence a patient's Oral Health-Related Quality of Life (OHRQoL). Due to drastic changes in children's dental, facial, and cognitive development throughout childhood and adolescence, measuring children's oral health-related quality of life (COHRQoL) has been challenging (10). Orofacial manifestations of OI which are not pathognomonic but can be distinct characteristics of the disease are dentinogenesis imperfecta (DI; brittle teeth), posterior open bite (lateral open bite), class III

skeletal malocclusion, posterior crossbites and impacted teeth (11). The severity of the oral manifestations varies across different types of OI such that the most severe cases have been observed in OI type III patients with high prevalence of craniofacial deformities and Dentinogenesis Imperfecta (DI) compared to OI types III and IV (12, 13).

Thanks to medical and surgical advancements in the past two decades, survival rates of patients with OI have substantially improved, leading to an increase in the prevalence of OI patients (14, 15). These advancements have also affected many aspects of OI patients' quality of life, mainly physical and functional aspects and, to some extent, their psychological state and social interactions (3, 16). Patients with OI may have their Oral Health-Related Quality of Life (OHRQoL) affected by the oral traits of the disease. This field has remained underexplored, and to the best of our knowledge, no study has evaluated OHRQoL amongst patients with OI.

Considering that children and adolescents are more prone to have a lower quality of life than adults, this thesis aims to discover the statistically significant determinants of OHRQoL amongst OI children. This thesis explores the extent to which oral health status indicators (Adjusted DFT and OHI-S) and oral characteristics of the disease (namely DI, class III malocclusion, lateral open bite and posterior cross bite) are associated with the OHRQoL in a convenience sample of children and teenagers with OI.

2. Literature review

The following section includes a comprehensive review of the literature on topics pertaining to Osteogenesis Imperfecta, its oral manifestations and Oral Health-Related Quality of Life and its determinants.

2.1 Osteogenesis Imperfecta (OI) – definition

Osteogenesis Imperfecta (OI), also known as "Brittle Bone Disease," merely means imperfect bone formation causing bone fragility and deformity.

2.1.1 History

The first recorded case with this condition belongs to a dislocated mummy of a child of ancient Egypt, dated from 21st / 22nd dynasty between 850- 1000 BC (17).

The French gynecologist and pathologist J.F.G.C.M. Lobstein in his book "Traite d'Anatomie Pathologique" published in 1833, described a condition which he called "osteopsathyrosis idiopathica" an unusual brittleness of bones mostly observed in children and elderly. The Dutch anatomist Willem Vrolik, in his "Handbook of Pathological Anatomy and Tabulae" published in 1849, has introduced the term "Osteogenesis Imperfecta" (OI) to describe a newborn infant that died three days after birth with numerous fractures, which is known today as OI type II (Sillance classification). Therefore, Vrolik's disease (syndrome) was among various other common alternative names (ex. Rachitis congenita, Osteoporosis foetalis, Osseous fragility, etc.) given to this condition. For many decades "osteogenesis imperfecta congenita" and "osteopsathyrosis idiopathica" were assumed to be two different diseases related to Rickets. It was until 1897 that histological examinations by Schmidt, showed similarities between osteopsathyrosis and OI. Originally three principal symptoms have been described for the disease: bone fragility, blue

sclerae, and deafness. Initial classification of the disorder considered numerous fractures before birth (in uterine life) as the severe form of the disease and called it “osteogenesis imperfecta congenita” (Vrolik’s syndrome) and fractures after birth as the milder form and called it “Osteogenesis imperfecta tarda” (18, 19). In 1979 Sillence et al. proposed the current four type classification based on the severity of bone fragility and different clinical manifestation of the disease (20).

2.1.2 Classification

OI has first been classified by Sillence et al. in 1979 (20) on the basis of phenotypical differences (mainly degree of bone brittleness), radiographic features and mode of inheritance into four types; I-mild, II-neonatally lethal, III-severe, progressively deforming and IV-moderately severe (severity between OI type I and III) (21, 22). Mutations occurring in different regions of the same genes encoding for COL1A1 or COL1A2 proteins can result in OI with various severity (clinical outcome). Hence, for the sake of convenience, they have been all classified into type I to IV on the basis of severity in clinical manifestation. The severity of which increases in the order type I < type IV < type III < type II (lethal) (1, 20).

The Sillence classification has been expanded to more than sixteen types by different research groups based on recent discoveries in new genetic mutations, distinct clinical features, histological factors, and inheritance pattern (23). OI types I to IV accounts for almost 90% of all OI cases and the other types are extremely rare (16).

2.1.2.1 OI Type I

OI Type I exhibits milder version of OI manifestations for which it has been called “mild OI.” It has an autosomal dominant inheritance pattern, and the mutation are in genes encoding for COL1A1 or COL1A2 proteins (mutations in heterozygous or homozygous null COL1A1 or

COL1A2 genes) (15, 16). It is caused by insufficient amount of type I collagen production (quantity inadequacy) which can result in mild bone fragility, blue sclerae, near-normal stature, and late-onset hearing loss. The key point is that dentinogenesis imperfecta exists in these patients, but it is not always clinically obvious, and it should be confirmed by radiographs. Patients with OI type I also have slight joint elasticity, and poor muscle tone compared to individuals without OI (15).

2.1.2.2 OI Type II

Infants with type II OI die before birth or within the first two weeks of life hence, it's been called "perinatally lethal OI." The main reason for death is severe bone deformity that can cause respiratory failure. It has an autosomal dominant inheritance pattern, and the mutation has occurred in genes encoding for COL1A1 or COL1A2 proteins. The resulted collagen is distorted (quality deformity) and produced in insufficient quantity.

2.1.2.3 OI Type III

Patients who suffer from OI type III exhibit the most severe manifestations of the disease amongst living OI patients. It also is called "progressively deforming OI" as it gradually develops the severe traits of the disorder throughout life. It has an autosomal dominant inheritance pattern, and the mutation has occurred in genes encoding for COL1A1 or COL1A2 proteins. The amount of collagen is sufficient, but there is a primary structural defect in them which has more severe consequences (2, 24). OI type III is characterized by extremely fragile bones, severe bone deformity (bowed bones), dentinogenesis imperfecta, very short stature with scoliosis (spinal curvature) and barrel-shaped rib cage, triangular face, early loss of hearing, poor muscle tone with loose joints and more importantly respiratory problems. Due to aforementioned characteristics,

these patients are severely handicapped, and almost all of them employ wheelchair as a mean of transportation.

2.1.2.4 OI Type IV

When the disease severity (mainly bone fragility) falls somewhere between OI type I (mild) and type III (severe), Sillance et al. had classified them as moderate OI (type IV). Bone fragility and deformity is mild to moderate, and they have moderate growth retardation. Genes encoding for COL1A1 or COL1A2 proteins are involved, and they have an autosomal dominant inheritance pattern. They present almost all typical signs of the disease including bone deformity (bowed bones), blue sclera (mostly normal, fades with age), Dentinogenesis Imperfecta (DI), hearing loss, etc. Type I collagen in these patients is impaired both in quality (deformed structure) and insufficient quantity. Patients with OI type IV are usually confined to canes or walkers for transportation (3, 16).

2.1.2.5 Other Types of OI

New advancement in genetic understanding of OI, has dictated the shift from a more clinical based approach classification (Sillence type I- IV) towards a genetic-functional approach in which the Sillience types I- IV are constrained to mutations in genes encoding COL1A1, and COL1A2 and new genes are given supplementary type numbers based on the mutation regardless of physical correlation (types V- XVI). These types predominantly have an autosomal recessive inheritance pattern (except type V), and they account for less than 15% of cases having OI which makes them extremely rare.

2.1.3 Epidemiology

Osteogenesis imperfecta is a heterogeneous, heritable, pan-ethnic and non-gender specific systemic disorder of bone with a cumulative incidence of one in 15–20 000 births (16). It is

estimated that there are approximately 25,000 to 50,000 affected individuals in the United States. The prevalence of OI is approximately 8 per 100,000 people worldwide which makes it a rare disease (21, 25).

Population prevalence deemed to be higher in OI type I compare to type III with the ratio of 7 to 1, based on a study on white Australians. For unknown reasons, this figure is reverse for black population living in South Africa, with an estimated minimum population frequency of approximately 0.6 for OI type III and 0.1 for OI type I per 100,000 (25).

2.1.4 Pathophysiology

Osteogenesis imperfecta is a predominantly collagen-related disorder that originates from different genetic mutations resulting in fragile bone, employing distinct metabolic pathways. In general, there are two categories of mutations which cause OI: 1) mutations in the genes encoding proteins responsible for synthesis, processing, secretion and post-translational modification (folding and cross-linking) of type I collagen (OI type I- IV) and 2) mutations in the genes encoding proteins participating in differentiation process (cell development) as well as bone mineralization activity of osteoblasts (bone-forming cells, OI type V- XVI). Clinical evidence of the mutation may remain hidden for many years despite the existence of disorder from birth. OI is an inherited disorder, mostly transmitted as an autosomal dominant genetic trait (85- 90% of cases), due to mutation in type I collagen genes (COL1A1 or COL1A2) that result in quantitative reduction (OI type I) or structural deficiency (OI type II-IV) in type I collagen. Another rare autosomal dominant mutation in the genes coding for interferon-induced transmembrane protein 5 (IFITM5) induce an increased ectopic endochondral bone ossification, specifically in the forearms, making it difficult to turn the wrist (OI type V) (15, 16).

Recent discoveries in the past ten years concerning causative genes, protein chemistry, and molecular biology has revealed more than twelve distinct mutations with different metabolic pathways having autosomal recessive inheritance exhibiting OI characteristics (OI type VI- XVI), meaning that it requires mutated genes from both parents (15, 16, 24). Spontaneous (sporadic) mutations*, or non-inherited mutation, is known to occur in rare cases (24).

2.1.5 Manifestations

2.1.5.1 General characteristics

OI can be characterized by different frequencies of bone fractures depends on the mutation and skeletal abnormalities such as short stature with macrocephaly, long bone bowing, flat midface and triangular facies, dentinogenesis imperfecta, barrel shape chest and scoliosis along with non-skeletal features like blue sclera, hearing loss, and pulmonary function deficiency. (1, 16).

2.1.5.2 Dental and oral manifestations

Osteogenesis imperfecta is a well-known disease for its effect on bones fragility. Additionally, OI can affect the teeth structure, growth pattern of the jaws and also dental development, causing orofacial alterations including:

2.1.5.2.1 Dentinogenesis Imperfecta (DI)

Dentinogenesis imperfecta is a genetic disorder of tooth development causing discolored teeth (yellow-brown or blue-gray hue) with a weak structure that rapidly wear (only on decidious teeth), fracture and ultimately results in tooth loss (11, 12, 26). The tooth enamel has normal structure but weakness in dentin construction caused by dentin dysplasia causes the enamel to chip off and the

* All the genetic disorders are spontaneous mutation in the first place but the argue is how that mutation will get inherited to the offspring.

remaining dysplastic dentin then wears down rapidly. This condition is inherited in an autosomal dominant pattern and classified into three types.

DI type I is associated with OI. It affects both primary and permanent teeth, but primary teeth are more severely affected compared to permanent dentition (22). Radiographic features of OI-related DI (DI type I) includes bulbous crowns with marked cervical constriction, short and slender roots, progressive pulp chamber and root canals obliteration. Golden standard test to confirm the presence of DI is histological examinations, meaning that lack of clinical and radiographic signs of DI does not imply the absence of DI. Histologically, irregular dentinal tubules with uncalcified matrix areas are observed. Depending on the severity of the disease, on average 28% to 73% of patients with OI exhibit DI type I with higher prevalence in OI type IV and III. Treatment methods to restore dental function and esthetics along with preserving patients vertical facial dimension includes stainless steel crowns for primary dentitions and full crowns or veneers for permanent teeth (12, 27).

2.1.5.2.2 Class III malocclusion (Craniofacial abnormality)

As per Edward Angel classification, perfect dental occlusion/relationship is obtained when the mesiobuccal cusp of the upper first molar be aligned with the buccal groove of the mandibular first molar. For any reason (skeletal or dental discrepancies), if mesiobuccal groove of mandibular first molar falls anterior to the mesiobuccal cusp of maxillary first molar it is recognized as class III malocclusion. Simply, when the lower jaw is located in front of the upper jaw in the anteroposterior dimension its called class III malocclusion. This discrepancy is mainly attributed to the alteration is the size and/or position of the upper jaw or the lower jaw.

Children with OI present an edge to edge occlusion in their primary dentition, but gradually as a result of an increased mandibular prognathic pattern and maxillary hypoplasia, the dental relation

between upper and lower jaw will evolve to become a class III malocclusion (11, 12). This malocclusion is mostly associated with anterior crossbite (over 60%) due to a reverse overjet caused by the underdeveloped nasomaxillary complex in both sagittal and vertical plans and overdeveloped mandible in sagittal plan leading to clockwise rotation of the mandible (12, 27).

2.1.5.2.3 Posterior cross bite

OI patients manifest a unique growth pattern that results in a non-functional posterior cross-bite. Other than the reduction in maxilla's size in all dimensions (length, height, and width) OI patients present an enlarged mandibular dentoalveolar process which is more evident in the molar area and causes this discrepancy (12, 27).

2.1.5.2.4 posterior/lateral open bite (Dental development)

This phenomenon has documented years before bisphosphonate therapies and happens only in the posterior areas while the anterior teeth are not affected. Children with OI exhibit lateral open bits (mostly amongst OI type III), and it was independent of DI status or bisphosphonate consumption. It has been suggested that lack of dentoalveolar process vertical development in coordination with high prevalence of impacted upper second permanent molars (27 to 33% of OI children) are the etiology of this manifestation. These open bites can seriously hinder the patients chewing capabilities (11, 12, 27).

2.1.6 Diagnosis

The primary diagnosis of OI is based on clinical and radiographic findings. Hallmark characteristics of OI are susceptibility to bone fractures following a mild trauma, bow shape deformity of long bones, and growth deficiency. Additionally, the presence of blue sclera and dentinogenesis imperfecta are of diagnostic value. Diagnosis of patients presenting typical features of OI or having a positive family history is not hard. However, cases with no family history whom

their bone brittleness is not associated with any classic characteristics of OI is hard to diagnose. Patients undergone child abuse and adults suffering from early onset of osteoporosis often have similar manifestations as mild osteogenesis imperfecta (OI type I), as both may have multiple fractures in various stages of healing and differentiating them is essential. One good diagnostic measure is dual-energy x-ray absorptiometry (DXA) which helps clinicians to distinguish them by their bone density level. Histologically, bones are low in volume and trabecular number with high turnover kinetics which does not provide useful information for diagnosis except in OI types V and VI which have distinct histology with fish scale appearance of the lamellar bone pattern (15, 16).

Quality and quantity of type I procollagen molecules can also get evaluated by skin biopsy (fibroblasts) which can help in diagnosing the autosomal dominant forms of OI (type I-V). The best confirmatory test to rule out OI is DNA testing. Full screen of causative genes has been recommended to check for secondary mutations, identify carrier status and to understand the complexity of the disorder (15, 16).

2.1.7 Management

There is no cure for the disease. Thus, the term treatment has been replaced by “disease management” in the literature, stating it can get best managed by a multi-disciplinary approach. Management of OI is symptom-based and rely upon the severity of the manifestations, and it can be categorized into three groups: medical management, surgical management, and rehabilitation strategies. All of which their ultimate goal is to enhance the quality of life (QoL) of OI patients.

2.1.7.1 Medical management

Bone strength relies upon three elements namely bone mass (quantity), bone material property (quality) and bone structure (distribution). Patients with OI have an adequate amount of bone

material, but the embedded problem is that the bone matrix is hypermineralized (less flexible) and highly disorganized (structural deficiency). Anti-resorptive (bisphosphonate) and anabolic (ex. Human growth factor) pharmacological therapies have been developed to strengthen bone by increasing the bone mass (quantity), which can decrease the fracture rate related to the disease and subsequently reduce pain. Bisphosphonates and other anti-resorptive drugs (synthetic analogs of pyrophosphate) can successfully enhance bone resistance by reducing bone turnover increasing bone volume and ultimately a significant decrease in fracture rate (28). Bisphosphonates are stable analogs of pyrophosphates that have antiresorptive properties. Maximum bone density and histology benefits from bisphosphonate are known to get obtained after three years consumption. Intravenous (IV) infusion of bisphosphonate (specially Pamidronate) is the current treatment of choice, due to poor bioavailability of bisphosphonate via the oral route (29).

2.1.7.2 Surgical management

Orthopedic interventions have been employed to provide strength, stability, and alignment to malformed brittle bones and one can be classified into two general groups; upper and lower extremity rodding and spinal fusion surgeries. The best surgical choice for upper and lower extremity reinforcement is intramedullary rodding which enhance stability and alignment by inserting stainless steel rods into intramedullary canals of long bones without using plates and screws as it increases the probability of fracture. Patients having Scoliosis with spine curvature greater than 50˚are candidates for spinal fusion surgery to initially stabilize their current situation and if possible partly correct the curvature (3, 16).

2.1.7.3 Rehabilitation strategies

Many strategies have been employed with the hope of maintaining and enhancing the extent of autonomy in patients with OI. Initially by weight-bearing activities and physical aid equipment

like canes, crutches, walkers or in extreme cases mobility devices like manual or powered wheelchairs. Simultaneously, holding special physical and educational programs to perform stretching on targeted joints and muscles followed by special instructions about how to stay physically fit and that promote a healthy lifestyle. Complementary to strategies above, environmental adaptation to the home, school or workplace will enhance their independence.

2.2 Oral health-related quality of life

2.2.1 Quality of Life – definition

Quality of life depicts patients' perception of functional limitation, psychological problems, social communications and other aspects of life affected by the illness (14). The World Health Organization (WHO) defines QoL as the "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" (30). This broad concept circumscribes many different components of well-being (e.g., physical, psychosocial, emotional) and overall health (31).

2.2.2 Health-Related Quality of Life

The notion of health-related quality of life (HRQoL) has started to arise in the late 1960s (32). Following an evolution in perceiving and defining health through time, a fusion of biomedical and socio-environmental models resulted in a radical shift from a disease-centered to patient-centered approach in defining and measuring health (9, 10). In 1948, the World Health Organization defined health as "the state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"(33). The term "health-related quality of life" (HRQoL) narrows QoL to aspects relevant to health. In other words, evaluation of HRQoL is essentially an estimation of QoL and its relationship with health (34).

Although the quality of life by definition encompasses health and despite their inherent correlation, but they are conceptually and empirically different (31). Locker proposed that health issues may affect the quality of life, but such a consequence is not inevitable (9). Evidence provided by Albrecht and Devlieger (35) shows that despite the extreme physical limitation, patients suffering from chronic conditions have reported having good QoL. This phenomenon which they called it "disability paradox" reveals the conceptually and empirically distinction between health and quality of life (31). Therefore, the term "health-related quality" of life was introduced to better differentiate between these two concepts and focus on the impacts of health and illness on quality of life (36).

2.2.2.1 Health-Related Quality of Life amongst OI patients

Patients with OI experience physical limitations due to the disorder's manifestations. Physical restraints affect their independence, self-image, social development, and lifestyle. The magnitude of this impact mostly relies upon the severity of the disorder, its natural history and family history of the disease (presence of other affected family members) (37).

Knowing that there is no cure for the disorder, OI patients, and their families are mostly concerned about the natural history of the disease. Therefore, it is of particular importance to comprehend the psychosocial aspect of this life-long condition. Ambulation ability, presence of contracture, and presence of secondary deformity (ex. Bowing of long bones, scoliosis, etc.) determines the functional status of OI patients (5, 37). Studies have also shown a majority of OI patients recognize dental problems (pain caused by food mastication), back pain, and hearing deficits to affect their health (37).

Bisphosphonate therapy, both orally and intravenous injection (Pamidronate) have shown to be significantly effective in increasing bone mineral density (BMD) and decreasing fractures which

lead to an improvement in almost all QoL markers (38). Worth mentioning, bisphosphonate has not shown a significant increase in the functional ability of these patients (14).

Owing to medical and surgical advancements in the past two decades, survival rates of patients with OI has substantially improved which increased the prevalence of OI patients. It also affected many aspects of patients' quality of life, mainly physical and functional aspects and to some extent their psychological state and social interactions (14).

2.2.3 Oral Health-Related Quality of Life

It was not till the early 1980s when the perception of the profound impact of oral diseases on general health and consequently on QoL resulted in the evolvement of the new concept called oral health-related quality of life (OHRQoL) (32). The term "oral health-related quality of life" (OHRQoL) focuses on physical, psychological, and social impacts of oral conditions (oral health disparities) on overall health and QoL of individuals. Oral health affects general health by generating pain, changing what individuals eat, and how they grow, look, speak, chew, taste food, socialize, enjoy life, and their feeling of social well-being. (8, 9). It should be noted that studies have shown a robust and inseparable relationship between perceived HRQoL and OHRQoL. The OHRQOL is a multidimensional concept that captures people's perception of elements related to their oral and craniofacial conditions that are important in their life. Employing OHRQoL as an evaluative outcome measure agrees with patient-center care (32, 39). The OHRQoL instruments are appropriate and sensitive for all individuals suffering from a health condition that has oral health manifestation. Due to drastic changes in children's dental, facial, and cognitive development throughout childhood and adolescence, measuring children's oral health-related quality of life (COHRQoL) has been challenging (10).

Oral and dental diseases are the most common of the chronic diseases (40) and have a significant effect on many aspects of individuals lives such as oral functions (physical), economy, social interactions, and psychological well-being (mental and emotional state) (41). “People assess their HRQOL by comparing their expectations and experiences” (42). QoL is a highly individual concept. Depending on many elements including age, gender, background culture, adaptive capacity, personal characteristics, life experience throughout life, etc., people have different expectations and perception of health which needs to be evaluated on an individual basis (32, 43). This demonstrates the importance of patients centered measures of oral health status. Allison and colleagues explained the critical role of time and experience and their impacts on humans’ attitudes and perceptions and further discussed how they could be modified by individuals coping skills, ability to adapt and level of expectations (44). Allison and colleagues have further discussed the difficulties in measuring health-related quality of life by arguing even if one can adjust for the potential confounders of this evaluation (age, gender, race, etc.), there would still be three inherent complications. The primary issue is that people have different expectations in their lives, as expectations are formed by previous experiences, and as people have different experiences throughout life, therefore level of expectations are highly specific. Secondly, the value measured for OHRQoL may change with time as the impact of the disease on QoL changes during the individual’s illness trajectory, so it depends on when the measurement is made. Finally, as the new experiences modify the level of expectations, thus the reference value of individuals expectation may vary over time. This highlights the fact that quality of life is a dynamic construct and attempts to quantify the QoL will result in an inherent uncertainty in its meaning (42).

To evaluate OHRQoL in accordance with the definition of health declared by WHO, it was a necessity not to be confined to clinical indicators (dental caries, periodontal disease, etc.) but also

incorporate other aspects of well-being particularly mental and social health. OHRQOL has been defined as “a multidimensional construct that reflects (among other things) people’s comfort when eating, sleeping, and engaging in social interaction; their self-esteem; and their satisfaction with respect to their oral health” (45). This recently emerged concept demanded new health status measures, unlike clinical measures of disease status. Subsequently, numerous alternative qualitative and quantitative methodologies have been developed to evaluate OHRQoL. “People assess their HRQOL by comparing their expectations and experiences” (42). QoL is a highly individual concept. Depending on many elements including background culture, life experience throughout life, etc., people have distinct expectations and needed to be evaluated on an individual basis (32). This demonstrates the importance of patients centered measures of oral health status. Studies have reported the dental alteration to be significant perceived health problem amongst OI patients. Sillence et al. found

hearing deficit, and back pain to be the most common physical discontentment. Findings from Other studies recognized dental problems to be the most prevalent health problem (60%) amongst OI patients with more frequency in severe OI types (37).

2.2.4 Oral health-related quality of life assessment

Generic oral health-related quality of life measures (ex. OHIP, CPQ, etc.) will get employed to assess OHRQoL in healthy individuals with common oral diseases (tooth decay, dental crowding, etc.). However, to enhance the sensitivity and reliability, disease condition-specific instruments were developed and adopted to evaluate OHRQoL amongst individuals having chronic diseases with distinct oral and craniofacial manifestations (5, 6, 10).

Basically, there are three types of OHRQoL measures: social indicators, global self-ratings of OHRQoL, and multiple item questionnaires of OHRQoL. The most popular approach to measure

OHRQoL is through multiple items standardized questionnaires (quantitative) (32). The burden of oral conditions on the whole society (community level) gets evaluated through population surveys on social indicators such as number of days having restricted activities (school absence, work missed) because of their oral condition health. Global self-rating also known as single-item rating is another method to assess person's perception of their general oral health by means of questions having categorical responses ranging from "Excellent" to "poor." Growing demand for more specific measures has led to an increase in instruments evaluating OHRQoL, including both generic (overall oral health) or disease-specific instruments. All instruments comprised of a various number of questioned categorized into specific domains (dimensions), assessing the influence of oral conditions on different aspects of individual's QoL. The outcome of these questionnaires is commonly reported as a score variable including domain-specific and total scores, which signifies (depicts) the impact of oral health on different aspects and general QoL (32). The obtained information from these questionnaires allows the clinicians to better understand the impact of the oral health on individual's perception of QoL before the intervention. Moreover, it can measure the magnitude of received treatment's impacted on patient's perception of QoL by comparing the results of before and after intervention (46).

To date, several OHRQoL instruments have been introduced; These include the Oral Impacts on Daily Performances (47), Dental Impact on Daily Living (48), Geriatric Oral Health Assessment Index (49), Oral Health Quality of life Inventory (50), The Oral Health Impact Profile (OHIP) (51), Child Perceptions Questionnaire (CPQ) (52, 53). Although conceptually all of these measures are very much alike, they vary in their constituent domains, their scoring method and the number of questions within each domain (length).

2.2.4.1 Child Perceptions Questionnaire (CPQ)

The Child Perceptions Questionnaire is a valid and reliable generic multi-item instrument that has been widely used in research to measure OHRQoL (54-57). It is the first comprehensive self-report group of instruments developed for children and their parents (58, 59). This questionnaire was introduced by Jokovic, Locker, and colleagues in 2002 (52), and has been validated in numerous languages since its development (60-63). This instrument is designed to evaluate the impact of oral, dental and orofacial disorders on both individual (functional) and social (psychosocial) aspects of life (31). As the children's self-concept and health comprehension is age-dependent, Jokovic et al. developed three age-specific questionnaires for different age ranges based on their cognitive, emotional, functional, social and language development differences into children between 6 and 7 (CPQ_{6-7}), 8 to 10 (CPQ_{8-10}), and 11 to 14 (CPQ_{11-14}).

The development of this instrument took place in two stages process. Initially, a primary pool of 46 items was developed, consisting of questions collected from already existing oral health and child health status questionnaires. Second, the clarity, relevance, and comprehensiveness of these items were evaluated by an expert panel composed of child health professionals and parents of children with oral and orofacial disorders. A modified pool of 50 items was then developed based on their feedbacks. This was revised further following in-depth interviews with a small number of child patients. In order to meet the criteria for a patient-centered scale, an item impact study was performed to identify the items for the final questionnaire in a way that is important to the patients' population (52).

The measure was validated using the construct validity by extreme group approach. Here, the scores of three groups of patients with different conditions and severity (patients with dental diseases, orthodontic disorders, and orofacial conditions) were examined. The validity of the

questionnaire was further analyzed by examining associations between CPQscores, self-ratings of oral health and ratings of the extent to which the condition of the teeth and mouth affected on overall well-being. Statistical analysis revealed a stronger correlation between CPQscores and the rating of the impact of overall well-being (0.40) compared to CPQscores and self-rated oral health (0.23). This result indicates that the items in the questionnaire address issues that not only affects the oral health but also have some impact on life as a whole (31, 52, 58, 59).

3. Research Question and objectives

Osteogenesis imperfecta is a severely debilitating disorder which has been found to have a birth prevalence of 0.3-0.7 per 10,000 births, and estimations show approximately 20,000 to 50,000 people are affected by OI in united states (15, 24). Studies have shown that patients suffering from OI have lower physical QoL compared to healthy populations. Additionally, patients living with OI type III have lower QoL compared to OI type I. Patients with Osteogenesis Imperfecta (OI), may have their Oral Health-Related Quality of Life (OHRQoL) affected by the oral traits of the disease. This field has remained underexplored, and to the best of our knowledge, no study has evaluated OHRQoL amongst OI patients (4-6, 64, 65).

Considering that children and teens are more susceptible to have a lower quality of life than adults (6), the general aim of this thesis is to generate knowledge regarding the oral health status, oral and craniofacial manifestations, and oral health-related quality of life amongst children and teenagers between 8 and 14 having OI.

To gain insight into this topic, we employed a quantitative research approach to investigate the following question:

- To what extent oral characteristics of the disease (mainly DI, class III malocclusion, lateral open bite and posterior cross bite) are associated with the OHRQoL amongst a population of children and teenagers with OI.

The specific objectives are:

1. To explore oral health status amongst children having different types of OI.

2. To investigate oral and craniofacial manifestations of the disease and their frequency amongst children with different types of OI.
3. To assess the perceived OHRQoL in children having different types of OI.
4. To evaluate the extent to which oral and craniofacial manifestations of the disease are associated with negative impacts on OHRQoL amongst our convenience sample of children and adolescents suffering from OI.

4. Methods

4.1 Study design

Cross-sectional studies are observational studies in which data are collected on the entire study population at a single point in time, meaning that it measures prevalence, not incidence. There are two types of cross-sectional studies, one that aims to assess the frequency and distribution of a specific disease in a target population (descriptive study). The other one is called an "analytical cross-sectional study" that aims to evaluate the association between a potential risk factor and a health outcome. As in this type of study data on exposures, outcomes and confounders are collected simultaneously; therefore, this type of study is limited in its ability to draw credible conclusions about possible causality. Regardless, it is known to be efficient in studying the relationship between multiple outcomes and exposures and to generate hypotheses (66).

4.2 Study sites

This interim analytical cross-sectional study was conducted as a part of a longitudinal, multidisciplinary and multicenter hospital-based study with the objective of recording the natural history of the disease to improve the medical care and quality of life of individuals with OI. This study is being conducted in several specialized centers across North America (Houston, Montreal, Chicago, Baltimore, Portland, Washington DC, New York, Omaha, Los Angeles, Tampa). The research questions of this thesis are investigated employing a subset of data including all children and adolescents with any OI type for whom OHRQoL data were obtained in the first two study years from 6th of August 2015 to 3rd of August 2017.

4.3 Eligibility criteria

The eligibility criteria to enter the study were as follows: the participants should (i) be diagnosed with OI by molecular (DNA) analysis and/or their clinical history and radiographs be highly suggestive of OI (ii) be in the age range between 8 to 14 (iii) have no other skeletal dysplasias other than OI (iv) not have a second genetic or syndromic diagnosis other than OI.

4.4 Ethical approval and informed consent

Study participants were recruited through the Brittle Bone Disease Consortium (https://www.rarediseasesnetwork.org/cms/BBD) that comprises several specialized centers across North America (Houston, Montreal, Chicago, Baltimore, Portland, Washington DC, New York, Omaha, Los Angeles, Tampa). The study protocol was reviewed and approved by the ethical committees of at all participating study centers. The study obtained ethics approval from McGill ethics committee, number A09-M47-15B. Eligible patients were approached by a research assistant and after explaining the study protocol, all study participants or their legal guardians were asked to sign the informed consent form

4.5 Data collection

4.5.1 Recruitment procedure

One qualified and calibrated dentist with the help of an assistant at each site were responsible for patient recruitment and data collection. They were all trained by the principal investigators (PI) of their site on how to collect data and the study procedure. The eligibility of OI patients seen at the clinics was evaluated by the research assistance and eligible patients were asked to participate in the study.

4.5.2 participation rate

During the period of August 2015 to August 2017, a total of 138 individual (62% female) diagnosed with different types of OI participated in the study, out of 138 eligible patients, resulting in a participation rate of 100%.

4.5.3 Study instruments

4.5.3.1 Questionnaires

After obtaining informed consent, patients and their legal guardians went through a face-to-face interview with the research assistants, which lasted approximately half an hour. Three separate questionnaires were employed to collect information on baseline comprehensive medical assessment, demographics, and family history of OI. (Appendix- 1)

Prior to the dental examination, the participants' OHRQoL was evaluated using Child Perception Questionnaire (CPQ). There were two versions of CPQ based on the patient's age group, one for children between eight and ten years of age (CPQ_{8-10}) (Appendix- 2) (53), and one for teenagers aged between 11 and 14 (CPQ_{11-14}) (Appendix- 3) (52). After verifying the age of each subject, the corresponding CPQ questionnaire was administered, and they were asked to complete it unassisted by parents or investigators (67, 68). These questionnaires had been designed to evaluate the impact of oral and craniofacial conditions on QoL of individuals while considering the different stages of development and cognition (52, 53).

Patients were then accompanied to the clinics, where their craniofacial traits as well as oral hygiene (OHI-S) and oral health (e.g., decayed and filled teeth) were evaluated using the international criteria standardized by the World Health Organization for oral health surveys. Patients were examined on a dental chair in a room with natural light, using sterilized CPITN

probes and plane sterilized dental mirrors, after drying the teeth with non-sterilized gauze (69). In the clinical examination, hygiene condition, caries status, anteroposterior relationship, crossbite, open bite and DI status were evaluated. (Appendix- 4)

4.6 Quality assurance and data management

All the study procedures were administered strictly following the manual of operations (BBD7701 Dental 28Feb16) described in the interviewer's guide. (Appendix- 5) The research assistants' work was strictly monitored by each site's collaborators who were in regular correspondence with the principal investigators through the project coordinator in the University of South Florida.

Questionnaires and oral examination data were collected on paper and entered into online data capture system. The quality of data was assessed at the entry point using on-line case report forms. The Data Management and Coordinating Center (University of South Florida) identified missing or unclear data and generated data queries to the enrolling centers in addition to monitoring data delinquency to generate good-quality data.

4.7 Definition of variables and measures

The following section explains how outcomes and exposures were measured and variables of interest were computed.

4.7.1 Outcome variables (Oral Health-Related Quality of Life (OHRQoL) measures)

The Oral-Health Quality of Life Questionnaire assesses the impact of oral and craniofacial anomalies on the oral health-related quality of life. Prior to the dental examination, OHRQoL of patients was evaluated using Child Perception Questionnaire (CPQ). For the purpose of this study

we employed two different versions of CPQ, one for participants aged between 8 and 10 years (CPQ_{8-10}) and one for patients in the age range of 11 to 14 years (CPQ_{11-14}). After verifying the age of the participant, the research assistants provided them with the corresponding questionnaire which they then completed unassisted by their parents or the investigators.

4.7.1.1 Child Perceptions Questionnaire 11-14 (CPQ_{11-14})

The CPQ_{11-14} comprises 37 questions and consist of four health domains: oral symptoms (OS; N=6), functional limitation (FL; N=9), emotional well-being (EWB; N=9) and social well-being (SWB; N=13) related to oral health conditions (52). This instrument contain questions considering the frequency of events in relation to the condition of the mouth or teeth over the previous three months (CPQ_{11-14}). The responses to questions are scored on a frequency scale using the following response options and associated codes: 'Never = 0'; 'Once/twice = 1'; 'Sometimes = 2'; Often = 3', and 'Everyday/Almost every day = 4'. The questionnaires also contain two single-item global ratings. Additive subscale CPQ scores (domain specific score) are computed by summing response codes. Since each domain contains different numbers of questions, scores for each subscale varies accordingly; oral symptoms (0-24), functional limitation (0-36), emotional well-being (0-36) and social well-being (0-52). The overall CPQ scores are computed by adding up all four domain subscale scores together, and it may range between 0 to 148. Higher scores denote more significant negative impact of orofacial conditions on OHRQoL (52, 53, 57, 67).

4.7.1.2 Child Perceptions Questionnaire 8-10 (CPQ_{8-10})

The CPQ_{8-10} contains 25 questions which were selected from CPQ_{11-14} based on the child development literature and advice received from child psychologist, teacher of grades 3 and 4 and parents. These questions were finally reworded to be suitable for 8-year-old children (53). Similar to CPQ_{11-14}, questions are organized into four health domains related to oral health conditions, but

the difference is in the number of questions constituted each domain; oral symptoms (N=5), functional limitation (N=5), emotional well-being (N=5) and social well-being (N=10). Also, here the questions ask about the frequency of events in relation to child's orofacial condition in the previous 4 weeks. The scoring systems is identical to what explained above for CPQ_{11-14} questionnaire. Given different number of questions, the overall CPQ_{8-10} score ranges from 0 to 100 and correspondingly subscales scores range differently; oral symptoms (0-20), functional limitation (0-20), emotional well-being (0-20) and social well-being (0-40). Likewise, higher scores denote more significant negative impact of orofacial conditions on OHRQoL (52, 53, 57, 67). The validity, reliability, and responsiveness of these measures have been established in various settings (70-75).

4.7.2 Explanatory variables (Dental and craniofacial clinical examination)

A comprehensive dental and craniofacial evaluations carried out by one calibrated dentist at each site in a dental clinical setting. Patients were examined on a dental chair in a room with natural light, using sterilized CPITN probes and plane sterilized dental mirrors, after drying the teeth with non-sterilized gauze (69). The dental assessment included; cavity status and oral hygiene assessments, checking for dental and intraoral anomalies, following with an exploration of dental occlusion, looking for discrepancies or abnormal relationships between jaws in all dimensions.

4.7.2.1 Cavity status (Adjusted-DFT)

Caries status has measured using DFT instead of DMFT to overcome potential inaccuracies in determining the cause for missing teeth (missed due to caries or oral trait of OI), based on the International Caries Detection and Assessment System (ICDAS) measurements (76). Furthermore, due to the statistically significant difference between numbers of teeth present in the mouth amongst different OI types (Table 5.1 & 5.3), caries status of patients was recorded employing

Adjusted-DFT. This index controls for the number of teeth by dividing the DFT score by the number of teeth presented in individuals mouth (value between zero and one). This mathematical modification helps increase the accuracy of comparing caries status between different types of OI (77). In this convenient sample of participant aged between 8 and 14, there are individuals with either primary or permanent dentition or a mixture of both. All subjects in the deciduous, mixed and permanent dentition stages were compared in the analyses using Adjusted DFT while no adjustments were needed in deciduous or permanent teeth in caries experience calculations. (Appendix V)

4.7.2.2 Dental (oral) hygiene status (OHI-S)

Oral Hygiene was assessed on participants according to the criteria established in the debris index of the Simplified Oral Hygiene Index (OHI-S), which is a value between zero and three. In this index, instead of assessing all surfaces of all teeth, specific surfaces of particular anterior and posterior teeth are selected (according to the age of the patient) for hygiene assessment. Since participants in this study belong to two different dental-age group, distinct set of teeth and surfaces were evaluated according to criteria defined for OHI-S index. One for children between 7 to 10 years of age and the other for patients over 11 years of age. Selected area for participants aged 7-10 years were as below:

- Posterior teeth - The buccal surfaces of the upper right first primary molar (tooth 54) and upper left permanent first molar (tooth 26) and lingual surfaces of the lower left second primary molar (tooth 75) and first permanent lower right molar (tooth 46) were examined.
- Anterior teeth - The buccal surfaces of the upper left primary central incisor (tooth 61) and lower right primary lateral incisor (tooth 82) were assessed. If any of the teeth were missing,

the corresponding tooth on the opposite side of the midline was used. Selected areas for the older age group are as followings:

- Posterior teeth - The buccal surface of the permanent upper first molars (teeth 16 and 26) and the lingual surface of the permanent first molars (teeth 36 and 46).
- Anterior teeth - The buccal surfaces of the permanent upper right and lower left central incisors (teeth 11 and 31) will be examined. If the permanent upper right or lower left central incisor is missing, the central incisor on the opposite side of the midline was used.

Oral hygiene of patients was evaluated and scored based on a quantity criterion using the following criteria and associated codes: 'No debris= 0'; 'soft debris covering up to one third of the tooth surface=1'; 'soft debris covering up to two third of the tooth surface=2'; 'soft debris covering more than two third of the tooth surface= 3'. Finally, an average score per number of surfaces scored was computed. Mean debris score presented by OHI-S was then classified into three categories: good (OHI-S< 0.99), fair (1<OHI-S< 1.99) and poor (OHI-S>2) (78). (Appendix V)

4.7.2.3 Dental occlusion

Assessment of dental occlusion in our study comprised of dental relationships (molar and canine classification), overbite, open bite (anterior or posterior), dental midline deviation, and crossbites (anterior and posterior).

The anteroposterior relationship was determined by the intercuspation of the permanent molars and classified as Class I (the mesiobuccal cusp of the maxillary first molar aligns with the buccal groove of the mandibular first molar), Class II (the mesiobuccal cusp of maxillary first molar occludes anteriorly to the mesiobuccal groove of the mandibular first molar), and Class III (The mesiobuccal cusp of the maxillary first permanent molar occludes posteriorly to the mesiobuccal groove of the mandibular first molar). Anterior crossbite was recorded when the maxillary incisors

were in palatal position relative to the mandibular incisors. Presence of an anterior open bite was documented in subjects with no contact between the anterior teeth when the posterior teeth were in maximum intercuspation. Posterior crossbite was recorded when the maxillary molars were occluded in a lingual relationship with the mandibular molars in centric occlusion. Posterior open bite (lateral open bite) was recorded in subjects with no contact between premolars teeth when the anterior teeth and first molars were in occlusion (11, 12, 79).

4.7.2.4 Dentinogenesis Imperfecta

DI was recorded in patients with a variable blue-gray to yellow-brown discoloration in their clinical teeth appearance, along with bulbous crowns, cervical constriction, thin roots, and early obliteration of root canal and pulp chambers apparent in the radiographs (11, 12, 79).

4.7.2.5 Additional variables

Sociodemographic characteristics of patients like age, gender, race, and their insurance status were collected as categorical variables. Medical and physical conditions including family history of OI, having chronic pain throughout body, taking any format of bisphosphonate, using wheelchair as a mean of transportation (categorical variables) and days missed school (count variable) were also recorded.

4.8 Missing data

Out of 138 subjects (56 children 8-10 and 82 teenagers 11-14), 8 (6%) participants had missing information on their CPQ scores, which was caused by missing scores in questions comprising the questionnaire. These unanswered questions were then replaced by the mode (most frequent answer) of the responses to that particular question across different types of OI employing single imputation method. Moreover, we had 5% missing values in variables obtained from dental and craniofacial evaluation that were replaced by the values retrieved from intraoral and extraoral

photographic evaluation forms and in 3 cases we used panoramic radiographs to substitute the missing values.

4.9 Overview of statistical analysis

All statistical analysis were performed with STATA-13 for windows (80). Along with the use of descriptive statistics to explore and test crude associations in the data, statistical models were employed in this study as described below.

4.9.1 Descriptive statistics

Descriptive statistics were performed to describe the crude features of the collected data. Univariate analyses (descriptive) were performed across different types of OI separately for each age groups (aged 8-10 (table 5.1- 5.2) & aged 11-14 (table 5.3-5.4)). Welch's t-test (independent samples t-test) was employed to handle the unequal variances and sample sizes between the groups of binary variables. When the sample size of a group was less than 15 patients, the Mann-Whitney U test (non-parametric) was performed to assess significant differences between the two groups. To determine the significant relationship between categorical variables, Chi-square test or Fisher's exact test for contingency tables with small cell counts have been employed.

4.9.2 Model specification

Multiple ordinal logistic regression was employed to evaluate the associations between oral and craniofacial characteristics and other explanatory (independent) variables and the outcome (dependent) variable (OHRQoL scores). Multiple ordinal logistic regression is a type of generalized linear model used to explain the extent of association between an ordinal dependent (outcome) variable and one or more independent variables by fitting a linear equation to the collected data. Ordered logit models have been derived by beginning with a binary logit/probit

model and generalizing it to allow for more than two outcomes (an outcome with more than two categories) (81).

In our study, patient's OHRQoL (CPQ-overall score) and its constituent domains (OS, FL, EWB, SWB) were the dependent variables, and they had been recorded as count variables (CPQ-scores). Also, oral condition variables, including oral health status and OI-related oral and craniofacial alterations, were the main exposures of interest.

In order to have more clinically significant results from our statistical analysis, the CPQ-score and their constituent subscale scores were transformed to ordinal variables (poor, fair, good) using their 33rd and 66th percentiles. Therefore, we were enabled to employ ordinal logistic regression to assess the extent of the impact that oral conditions, including disease-related oral and craniofacial traits, have on patient's perception of oral health quality of life, adjusting for potential confounders in the final selected model.

4.9.3 Model Construction using block-wise model selection strategy

To the best of our knowledge this is the first time that OHRQoL is being assessed in OI patients, and given that there is a strong and inseparable relationship between perceived HRQoL and OHRQoL (39), model selection was based on a mixture of prior knowledge obtained from HRQoL studies in OI patients (4-6, 82, 83) and theoretical assumptions over potential confounders.

First, a theoretical (hypothetical) framework (figure 4.1) is used to present a simplified conceptual model of associations of interest briefly and to illustrate relationships between the variables in the

study. Type of OI, sociodemographic characteristics and having family history were conceptually assumed to be confounder factors in the association of interest.

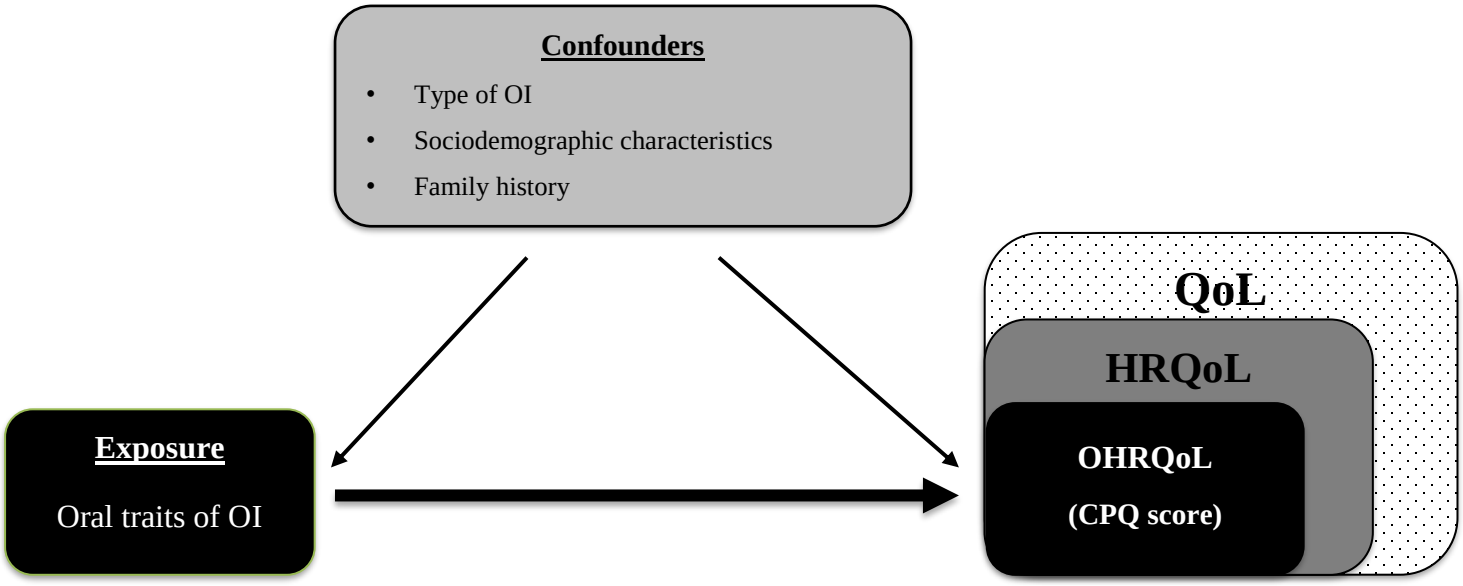

Figure 4.1 - Conceptual model of the associations between OI and the outcome (CPQ score)

Second, in order to explain the data in the simplest way, redundant predictors and confounders should be removed from final regression model. By doing so, we are eliminating the unnecessary variables that could add noise to the estimation of interest or cause collinearity (strong correlation between variables) in the model. To do so, block-wise model selection technique was employed to choose the set of potential confounders to include in the final regression model. By employing block-wise technique, initially it forces STATA to keep the key variables indicated by researchers in the model (forced entry method). Key variables are those which conceptually have an effect on the outcome (since we don't have prior knowledge) and therefore were not removed even if they were not statistically significant. Subsequently, other variables of interest (indicated in separate parentheses in the command) were introduced in the model and STATA will keep the statistically significant one in the model (data-driven method). For this procedure, STATA will create number

of different models, each comprised of the key variables and one of the additive variables in the command. Several created models will then be compared for their goodness-of-fit employing adjusted R square and Akaike's Information Criterion (AIC). Adjusted R square is a measure that presents the extent of variation in the outcome variable that can be explained by the explanatory variables, after adjusted for the number of variables in the model. Better model fit gets indicated by higher values of adjusted R square (84). AIC is another measure to test the fitness of the model employing the concept of deviance, and smaller AIC values depict better model fits (85, 86). As a rule of thumb, if two models have a difference in AIC ≤ 2, then the models are not different in their fit and under this circumstance the simpler model (model with less number of variables) will be employed as the final model (85). Type of OI, and gender was identified as the minimum set of potential confounders, to be included in the multivariate analyses. Therefore, the best fit model in this study comprised of the Outcome variable ($CPQ_{8\text{-}10,}$ $CPQ_{11\text{-}14}$ and their constituent domains), explanatory variables (adjusted-DFT, OHI-S, posterior crossbite, lateral open bite, DI, dental classification), and confounding factors (types of OI, and gender).

4.10 Sample size and power considerations

The data for this analysis included a convenience sample size of 138 observations (56 children and 82 adolescents). This is the largest sample size ever recruited on patients having OI (rare disease). This study is an interim evaluation of an ongoing cohort study (not concluded) and, therefore, statistical power has not been calculated for this outcome.

5. Results

5.1 Sample results

5.1.1 Response Rate

Out of 138 subjects (56 children and 82 teenagers), all of them agreed to participate in this study (response rate= 100%).

5.1.2 sample characteristics

A total of 138 aged 8-14 years (11.6 ± 2.1 years) having OI types I, III, IV, V and VI (n=65, 30, 37, 4 and 2, respectively) participated in the study. As the numbers of patients in OI categories of 'type V and VI' were limited, in order to have more statistical value they were merged and renamed as 'others.' Almost 62% of the total sample size (children and adolescents) were females and more than 79% Caucasians. The race categories of 'African American,' 'Chinese' and 'native American' were merged and renamed as 'others' due to limited numbers in these categories and to enable us for statistical analysis. All patients were living with their biological parents, and they were mostly attending school except six of them with OI type I, III, IV (n=3, 1, 2, respectively) and were homeschooled.

There were 56 children (22 boys and 34 girls) having OI types I, III, IV, V (n=26, 16, 12, 2, respectively) aged between 8 to 10 (9.4±0.8) years who complete the CPQ8-10 questionnaire and 82 teenagers (31 boys and 51 girls) with OI types I, III, IV, V, VI (n=39, 14, 25, 2, 2, respectively) within age range of 11 to 14 (13.2 ±1.1) years who filled out CPQ11-14 questionnaire. A detailed description of the sample characteristics can be found in Table 5.1 and Table 5.3.

5.1.2.1 Children aged between 8 to 10

In the children's group (Table 5.1), more children with OI types I and IV were having a parent or ancestor living with OI compared to OI type III (p-value <0.05). Using wheelchair as a mean of transportation was more prevalent in OI type III compared to OI type I and IV (p-value <0.05). Number of days which the child has missed the school due to his/her condition related to OI was significantly more prevalent in type III in comparison to type I (p-value <0.05) and also significantly higher in type IV compared to type I (p-value <0.05). No statistically significant difference was found in caries experience amongst children with OI (Adjusted-DFT). However, patients with OI type IV were showing statistically worse oral hygiene compared to OI type III. There were also more patients with DI amongst subjects having OI type III compared to both type I and type IV (p-value <0.05).

In the group of children (aged 8–10 years), there were no statistical differences in total scores of the CPQ8–10 or domain scores when different types of OI were compared (Table 5.2).

Table 5.1– Frequency distribution of individual characteristics, factors related to the disease, and oral conditions among children with different types of OI.

	OI I	OI III	OI IV	Others	All
Sociodemographic Characteristics					
Enrolment number – n (%)	26 (46)	16 (29)	11 (20)	3 (5)	56 (100)
Female	13 (50)	12 (75)	7 (64)	2 (66)	34 (61)
Age – mean (SD)	9.3 (1.0)	9.2 (0.9)	9.8 (0.5)	9.6 (0.5)	9.4 (0.9)
Race (White) – n (%)	22 (85)	13 (81)	5 (45) [c]	3 (100)	43 (77)
others	4 (15)	3 (19)	6 (55) [c]	0 (0)	13 (23)
Insurance status (Private) – n (%)	20 (77)	8 (50)	8 (73)	2 (67)	38 (68)
Medicare/Medicaid	6 (23)	8 (50)	3 (27)	1 (33)	18 (32)
Pertinent Medical and Physical Conditions					
Family history (Yes) – n (%)	19 (73) [a]	2 (12)	3 (21) [c]	3 (100)	27 (48)
Chronic pain in body (Yes) – n (%)	8 (31)	9 (56)	3 (27)	1 (33)	21 (37)
Bisphosphonate (Yes) – n (%)	11 (42)	16 (100)	11 (100)	3 (100)	41 (73)
Wheelchair use (Yes) – n (%)	1 (4) [a]	14 (88) [b]	4 (36) [c]	2 (67)	21 (38)
Days missed school – mean (SD)	9 (12) [a]	25 (24)	16 (14) [c]	29 (29)	16 (18)
Oral Conditions					
DFT – mean (SD)	2.6 (1.9)	4.1 (4.8)	2.1 (2.2)	3.0 (4.2)	2.9 (3.1)
Decayed – mean (SD) [b]	0.7 (1.3)	1.3 (1.9)	0.2 (0.4)	0.0 (0.0)	0.8 (1.4)

Filled – mean (SD)	1.9 (1.9)	2.8 (4.9)	2.1 (2.2)	3.0 (2.2)	2.2 (3.1)
Teeth – mean (SD)	23.1 (2.1)	23.9 (3.1)	21.9 (4.6)	26.0 (2.8)	23.2 (3.1)
Adjusted DFT _ mean (SD)	0.1 (0.1)	0.2 (0.2)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)
Low – n (%)	26 (100)	14 (88)	11 (100)	2 (100)	53 (96)
Moderate – n (%)	0 (0)	1 (6)	0 (0)	0 (0)	1 (2)
High – n (%)	0 (0)	1 (6)	0 (0)	0 (0)	1 (2)
OHI-S _ mean (SD) [b]	0.9 (0.6)	0.8 (0.4)	0.9 (0.2)	1.2 (0.3)	0.9 (0.5)
Good – n (%)	22 (85)	13 (81)	9 (82)	0 (0)	44 (81)
Fair – n (%)	1 (4)	2 (13)	2 (18)	1 (100)	6 (11)
Poor – n (%)	3 (11)	1 (6)	0 (0)	0 (0)	4 (8)
DI (Yes) – n (%)	5 (19) [a]	11 (69)	6 (55) [c]	0 (0)	22 (39)
Molar Malocclusion Classification – n (%)					
Cl I	11 (42)	3 (19)	1 (9)	0 (0)	15 (27)
Cl III	11 (42)	12 (75)	7 (64)	2 (67)	32 (57)
Cl II & mutilated	4 (16)	1 (6)	3 (27)	1 (33)	9 (16)
Posterior crossbite (Yes) – n (%)	9 (35)	6 (38)	3 (27)	2 (67)	20 (36)
Lateral open bite (Yes) – n (%)	4 (15)	7 (44)	2 (18)	1 (33)	14 (25)

Statistical tests) determine the significant relationship between categorical variables and OI types I, III and IV: Chi-square test or the Fisher's exact test for contingency tables with small cell counts; Compare means of a continuous variable between OI types I, III and IV: Welch's t-test for independent samples. As the sample size is small in each group (n<15), results have been confirmed by Mann-Whitney U test (non-parametric test).

[a] $p<0.05$ OI type I compared to OI type III.

[b] $p<0.05$ OI type III compared to OI type IV.

[c] $p<0.05$ OI type IV compared to OI type I.

Table 5. 2 – The Child Perceptions Questionnaire subscales for 8 to 10-year-old children (CPQ8–10).

OHRQoL	Number of items	Possible range	Observed range	OI I (n=26)	OI III (n=16)	OI IV (n=11)	Others (n=3)	Total (n=56)
Overall	25	0-100	0-43	10.0 (10.5)	9.8 (6.4)	9.0 (7.3)	9 (6.2)	9.7 (8.5)
Oral symptoms	5	0-20	0-15	4.9 (3.8)	4.8 (2.6)	4.4 (1.5)	5.3 (3.1)	4.8 (3.1)
Functional Limitation	5	0-20	0-8	1.3 (1.9)	2.6 (2.5)	1.4 (2.2)	2.0 (1.7)	1.7 (2.2)
Emotional Well-Being	5	0-20	0-20	1.9 (4.2)	1.7 (2.3)	1.7 (3.8)	0.6 (1.2)	1.8 (3.5)
Social Well-Being	10	0-40	0-13	1.8 (3.3)	0.7 (1.3)	1.5 (2.7)	1.0 (1.0)	1.4 (2.7)

Results are shown as n or mean (SD).
Statistical analysis: Welch's t-test, results have been confirmed by Mann-Whitney U test (non-parametric test).

[a] $p<0.05$ OI type I compared to OI types III.
[b] $p<0.05$ OI type III compared to OI types IV.
[c] $p<0.05$ OI type IV compared to OI types I.

5.1.2.2 Children and Teenagers aged between 11 to 14

In the adolescents' group (Table 5.3), more teenagers with OI types I were having a parent or ancestor living with OI compared with OI type III (p-value <0.05). Having chronic pain throughout the body was more prominent in OI type III compared to OI type I (p-value <0.05). Using wheelchair as a mean of transportation was more prevalent in OI type III compared to OI types I and IV (p-value <0.05). A number of days that teens missed school related to OI was significantly more prevalent in type III compared to type I (p-value <0.05) and also significantly higher in type IV compare to type I (p-value <0.05). Patients with OI type I were experiencing a higher number of decayed teeth compare to OI type III. However, since patients with OI type I were having statically significantly higher number of teeth in their mouth, therefore, no statistically significant difference was found in caries experience amongst teenagers with OI after adjusting for a number of teeth present in the mouth (Adjusted-DFT). Statistical analysis shows no significant difference in oral hygiene of patients having different types of OI amongst teenagers'. There were proportionally more patients with DI amongst subjects having OI type III compared to the other types, and this number is statistically significantly higher than OI type I (p-value <0.05). Subjects with posterior crossbites were found more to have OI type III in comparison to other OI types (p-value <0.05) and there were significantly more patients with posterior cross bite amongst OI type IV compare to OI type I (p-value <0.05).

In the group of teenagers (aged 11–14 years), total scores of the CPQ11–14 were significantly higher in OI types III or IV compared to type I (p-value <0.05 for both). When the sub-scales were compared, functional limitations had a greater negative impact on the OHRQoL of adolescents suffering from OI type III or IV (p-value <0.05 for both) when compared to those suffering from OI type I (Table 5.4).

Table 5.3 – Frequency distribution of individual characteristics, factors related to the disease, and oral conditions among teenagers with different types of OI.

	OI I	OI III	OI IV	Others	All
Sociodemographic Characteristics					
Enrolment number – n (%)	39 (48)	14 (17)	23 (28)	6 (7)	82 (100)
Female	22 (56)	11 (79)	14 (61)	4 (67)	51 (62)
Age – mean (SD)	13.2 (1.3)	13.4 (1.1)	13.1 (1.2)	13.7 (1.2)	13.2 (1.2)
Race (White) – n (%)	32 (82)	12 (86)	19 (83)	4 (67)	67 (82)
others	7 (18)	2 (14)	4 (17)	2 (33)	15 (18)
Insurance status (Private) – n (%)	26 (67)	9 (64)	14 (61)	3 (50)	52 (63)
Medicare/Medicaid	13 (33)	5 (36)	9 (39)	3 (50)	30 (37)
Pertinent Medical and Physical Conditions					
Family history (Yes) – n (%)	23 (59) [a]	1 (7)	7 (30)	3 (50)	34 (41)
Chronic pain in body (Yes) – n (%)	11 (28) [a]	10 (71)	9 (39)	4 (67)	34 (41)
Bisphosphonate (Yes) – n (%)	20 (51)	14 (100)	21 (91)	4 (67)	59 (72)
Wheelchair use (Yes) – n (%)	1 (3) [a]	13 (93) [b]	10 (43) [c]	4 (67)	28 (34)
Days missed school – mean (SD)	9.2 (10.4) [a]	17.1 (15.6)	27.2 (21.8) [c]	14.7 (13.8)	16.2 (17.1)
Oral Conditions					
DFT – mean (SD)	1.9 (3.1)	1.8 (1.7)	1.2 (1.6)	4.2 (6.5)	1.8 (2.8)
Decayed – mean (SD)	1.3 (2.9) [a]	0.2 (0.5)	0.4 (0.8)	3.3 (5.9)	0.9 (2.5)

Filled – mean (SD)	1.7 (2.9)	1.7 (1.4)	1.0 (1.54)	4.0 (6.7)	1.6 (2.7)
Teeth – mean (SD)	26.3 (1.7) [a]	23.0 (4.1)	25.3 (2.4)	26 (2.3)	25.4 (2.7)
Adjusted DFT _ mean (SD)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.2 (0.3)	0.1 (0.1)
Low – n (%)	36 (92)	14 (100)	23 (100)	5 (83)	78 (95)
Moderate – n (%)	3 (8)	0 (0)	0 (0)	1 (17)	4 (5)
High – n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
OHI-S _ mean (SD)	0.9 (0.5)	0.9 (0.3)	0.8 (0.2)	0.5 (0.1)	0.8 (0.4)
Good – n (%)	32 (82)	10 (71)	17 (74)	6 (100)	65 (79)
Fair – n (%)	5 (13)	4 (29)	6 (26)	0 (0)	15 (18)
Poor – n (%)	2 (5)	0 (0)	0 (0)	0 (0)	2 (3)
DI (Yes) – n (%)	4 (10) [a]	8 (57)	11 (48) [c]	2 (33)	25 (30)
Molar Malocclusion Classification – n (%)					
Cl I	22 (56)	0 (0)	5 (22)	3 (50)	30 (37)
Cl III	8 (20)	14 (100)	13 (56)	2 (33)	37 (45)
Cl II & mutilated	9 (23)	0 (0)	5 (22)	1 (17)	15 (18)
Posterior crossbite (Yes) – n (%)	5 (13) [a]	12 (86) [b]	11 (48) [c]	2 (33)	30 (37)
Lateral open bite (Yes) – n (%)	9 (23)	7 (50)	8 (35)	1 (17)	25 (30)

Statistical tests) determine the significant relationship between categorical variables and OI types I, III and IV: Chi-square test or the Fisher's exact test for contingency tables with small cell counts; Compare means of a continuous variable between OI types I, III and IV: Welch's t-test for independent samples. As the sample size is small in each group (n<15), results have been confirmed by Mann-Whitney U test (non-parametric test).

[a] $p<0.05$ OI type I compared to OI types III.

[b] $p<0.05$ OI type III compared to OI types IV.

[c] $p<0.05$ OI type IV compared to OI types I.

Table 5.4 **–** The Child Perceptions Questionnaire subscales for 11 to 14-year-old teenagers (CPQ11-14).

OHRQoL	Number of items	Possible range	Observed range	OI I (n=39)	OI III (n=14)	OI IV (n=23)	Others (n=6)	Total (n=82)
Overall	37	0-148	1-53	16.5 (12.8) [a]	24.7 (12.5)	23.1 (14.4) [c]	22.3 (17.7)	20.2 (13.8)
Oral symptoms	6	0-24	1-11	5.8 (2.9)	7.1 (3.2)	7.1 (3.2)	6.7 (4.3)	6.4 (3.1)
Functional Limitation	9	0-36	0-19	4.3 (4.2) [a]	8.6 (5.1)	7.2 (4.9) [c]	7.4 (5.9)	6.1 (4.9)
Emotional Well-Being	9	0-36	0-20	3.6 (5.7)	5.7 (5.9)	5.5 (6.9)	5.3 (7.2)	4.6 (6.2)
Social Well-Being	13	0-52	0-19	2.9 (4.7)	3.3 (3.8)	3.5 (4.5)	3.0 (3.1)	3.1 (4.3)

Results are shown as n or mean (SD).
Statistical analysis: Welch's t-test, results have been confirmed by Mann-Whitney U test (non-parametric test).

[a] $p<0.05$ OI type I compared to OI types III.
[b] $p<0.05$ OI type III compared to OI types IV.
[c] $p<0.05$ OI type IV compared to OI types I.

5.2 Regression analysis

As mentioned before, the final model selection (variable selection) was based on highest adjusted R^2 and lowest AIC values, after figuring out the best fit model. Since the outcome variables were transformed into an ordinal variable using 33rd and 66th percentiles as cutoff points, multivariate ordinal logistic regression was found to be the best fit model to evaluate the association between exposures and outcomes. There were five separate models for five outcomes including CPQ total score (OHRQoL) and its four constituent domains (OS, FL, EWB, SWB). Each model consisted of OI type, oral health status (Adjusted DFT and OHI-S) and OI-related oral conditions (DI, posterior crossbite, class III malocclusion, and lateral open bite), as well as gender, in addition to all other explanatory variables.

5.2.1 Regression analysis for OHRQoL in children group

Among children, a diagnosis with class III malocclusion was associated with a negative impact on OHRQoL. Children with class III malocclusion compared to those without, have 4.62 (95% CI: 1.11-19.32) times higher odds to have higher grades in oral symptoms domain (i.e. worse oral symptoms) of OHRQoL ($P<0.05$) after adjusting for confounders in the model. Having DI increases the odds of having worse OHRQoL by a factor of 2.87 (95% CI: 0.78- 10.51) ($p>0.05$). Children with posterior crossbite have 0.94 (95% CI: 0.27- 3.24) times higher odds to have worse OHRQoL ($p>0.05$). The same pattern of association was seen for other explanatory variables in the model, and all of them are inconclusive since they lack statistical significance (Table 5.5).

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Table 5.5 – Association between oral traits of OI and oral health-related quality of life in children aged 8- 10 years (CPQ8–10), adjusted for potential confounders.

	CPQ_{8-10} OR (95% CI)	Oral Symptoms OR (95% CI)	Functional Limitation OR (95% CI)	Emotional Well-Being OR (95% CI)	Social Well-Being OR (95% CI)
OI (Type I)	1	1	1	1	1
Type III	0.77 (0.18- 3.36)	1.16 (0.28- 4.73)	2.87 (0.65- 12.62)	1.75 (0.36- 8.25)	1.05 (0.18- 6.02)
Type IV	0.46 (0.09- 2.18)	0.55 (0.13- 2.45)	1.44 (0.31- 6.91)	0.94 (0.17- 4.96)	2.41 (0.35- 16.28)
Gender (Male)	1	1	1	1	1
Female	0.54 (0.16- 1.85)	1.48 (0.43- 5.09)	0.38 (0.09- 1.45)	0.76 (0.21- 2.87)	0.13 (0.03- 0.65)
Adj. DFT (percentage)	1.02 (0.97- 1.07)	1.01 (0.96- 1.04)	1.03 (0.98- 1.09)	1.02 (0.96- 1.09)	1.02 (0.97- 1.08)
OHI-S	1.13 (0.32- 4.04)	2.53 (0.63- 10.34)	0.88 (0.22- 3.55)	0.89 (0.22- 3.64)	0.27 (0.05- 1.62)
DI (No)	1	1	1	1	1
Yes	2.87 (0.78- 10.51)	1.35 (0.41- 4.48)	1.27 (0.35- 4.62)	1.95 (0.51- 7.62)	1.96 (0.45- 8.45)
Posterior cross bite (No)	1	1	1	1	1
Yes	0.94 (0.27- 3.24)	0.61 (0.18- 2.03)	2.07 (0.53- 8.16)	0.89 (0.23- 3.55)	2.08 (0.46- 9.46)
Molar classification (Cl I)	1	1	1	1	1
Cl III	2.67 (0.71- 10.11)	4.62 (1.11- 19.32)	0.58 (0.14- 2.34)	0.69 (0.16- 3.01)	0.94 (0.19- 4.59)
Lateral open bite (No)	1	1	1	1	1
Yes	2.46 (0.59- 10.24)	1.01 (0.26- 3.91)	3.06 (0.69- 13.62)	1.98 (0.42- 9.26)	3.05 (0.63- 14.95)

Results are given as Odds Ratio (95% Confidence Interval).

5.2.2 Regression analysis for OHRQoL in the teenage group

Having posterior crossbite amongst teenagers with OI increases the odds of having higher grades of functional limitations by a factor of 6.1 (95% CI: 1.7- 22.6) (Table 5.6). Moreover, when compared to those without posterior crossbite, teenagers with posterior crossbite have higher grades (denoting worsening) of oral symptoms (OR:5.1; 95% CI: 1.4- 18.1) and emotional well-being (OR:4.7; 95% CI:1.4- 16.1) after adjusting for the confounding factors in the model. A similar pattern of association was observed in social well-being domain of the OHRQoL scale, but it was not statistically significant. Accordingly, having posterior crossbite increases the odds of having lower OHRQoL by a factor of 5.9 (95% CI: 1.6- 20.9) amongst adolescents with any type of OI (Figure 6.2).

Also, adolescents having OI type III & IV compared to OI type I were 7.32 (95% CI: 1.2- 43.8) & 5.5 (95% CI: 1.6- 19.5) times more likely to have a higher score (indicating impairment) of functional limitations ($P<0.05$). When compared to OI type I, teenagers with OI type III and IV were 4.11 (95% CI: 0.76- 21.98) & 2.67 (95% CI: 0.82- 8.71) times more likely to have a higher score of CPQ_{11-14}, indicating worse OHRQoL. However, this association is not conclusive since it does not have statistical significance (Table 5.6).

Table 5.6 – Association between oral traits of OI and oral health-related quality of life in teenagers aged 11- 14 years (CPQ11–14), adjusted for potential confounders.

	CPQ_{11-14} OR (95% CI)	Oral Symptoms OR (95% CI)	Functional Limitation OR (95% CI)	Emotional Well-Being OR (95% CI)	Social Well-Being OR (95% CI)
OI (Type I)	1	1	1	1	1
Type III	4.11 (0.76- 21.98)	0.71 (0.13- 3.79)	7.32 (1.22- 43.82)	2.87 (0.53- 15.37)	1.11 (0.21- 5.86)
Type IV	2.67 (0.82- 8.71)	1.18 (0.38- 3.64)	5.55 (1.57- 19.55)	2.18 (0.65- 7.34)	2.11 (0.66- 6.75)
Gender (Male)	1	1	1	1	1
Female	0.85 (0.33- 2.21)	0.77 (0.29- 2.01)	0.67 (0.26- 1.75)	0.75 (0.28- 2.04)	2.08 (0.82- 5.26)
Adj. DFT (percentage)	1.01 (0.96- 1.05)	0.99 (0.95- 1.05)	1.03 (0.98- 1.08)	1.03 (0.97- 1.08)	1.03 (0.98- 1.08)
OHI-S	1.98 (0.67- 5.91)	1.78 (0.58- 5.43)	2.81 (0.84- 9.34)	1.76 (0.56- 5.53)	1.31 (0.48- 3.47)
DI (No)	1	1	1	1	1
Yes	0.65 (0.19- 2.13)	1.13 (0.37- 3.47)	0.27 (0.07- 1.01)	0.89 (0.26- 3.04)	0.95 (0.32- 2.93)
Posterior cross bite (No)	1	1	1	1	1
Yes	5.92 (1.67- 20.91)	5.14 (1.45- 18.15)	6.13 (1.67- 22.58)	4.71 (1.37- 16.08)	2.89 (0.87- 9.63)
Molar classification (Cl I)	1	1	1	1	1
Cl III	0.32 (0.08- 1.26)	0.54 (0.15- 2.04)	0.43 (0.11- 1.66)	0.35 (0.08- 1.45)	0.39 (0.11- 1.47)
Lateral open bite (No)	1	1	1	1	1
Yes	1.42 (0.46- 4.28)	0.77 (0.25- 2.28)	1.91 (0.58- 6.22)	0.92 (0.28- 2.96)	0.73 (0.24- 2.21)

Results are given as Odds Ratio (95% Confidence Interval).

***** Statistically Significant findings at $p<0.05$

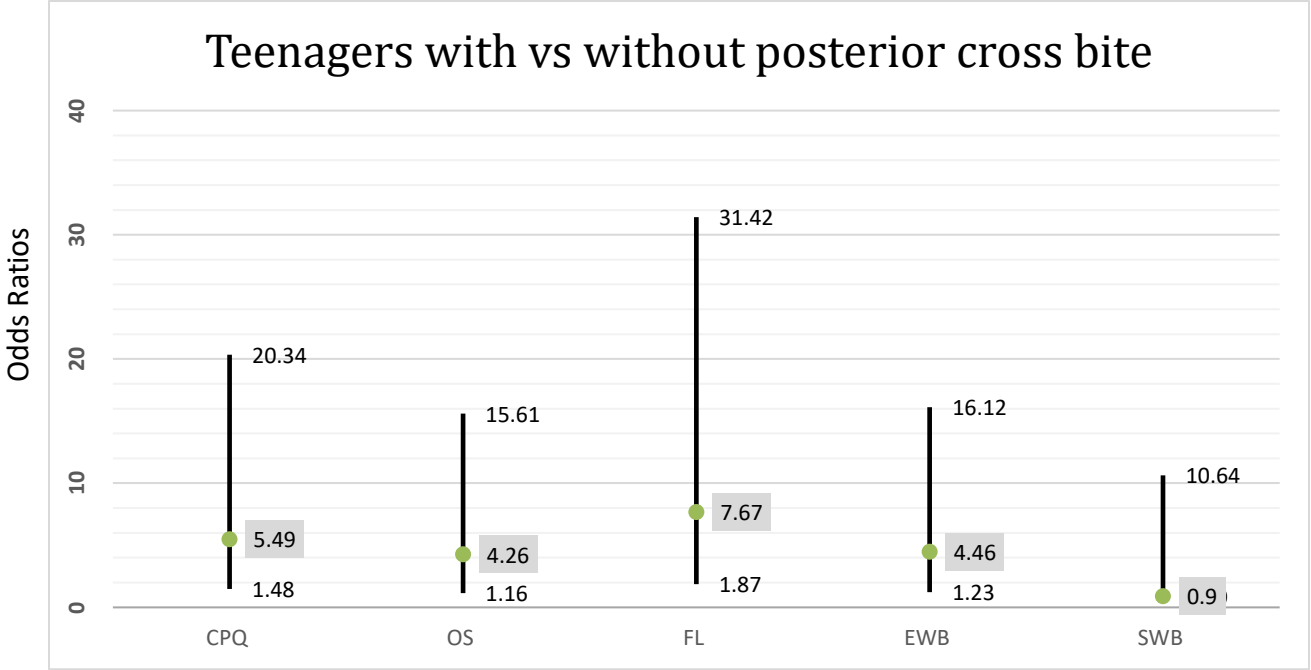

Figure 6.2- Association between posterior cross bite and CPQ total and domain scores

6. Discussion

6.1 Summary of research findings

This study was conducted to evaluate the extent of association between oral traits of OI and the oral health-related quality of life amongst children and adolescents having OI. This is the largest sample ever recruited on children and teenagers with OI and the variables controlled in the regression model are the minimum number of variables that potentially have confounding effect on the outcome. To the best of this author's knowledge, this is the first study in OI that has evaluated OHRQoL using a quantitative method. The CPQ questionnaire was chosen for this evaluation since, to date, it is the only comprehensive generic self-report oral health indicator for children. The age difference in cognitive, emotional, functional and behavioral characteristics of children has been accounted for in this child oral health status questionnaire. The CPQ has been modified accordingly to suit children within three age groups (1) children aged between 6 to 8 (CPQ_{6-8}) (2) children 8 to 10 years age (CPQ_{8-10}) (3) teenagers aged 11 to 14 (CPQ_{11-14}) (52). The OHRQoL is underexplored in OI populations, and this is the first attempt to evaluate oral health status in relation with their OHRQoL in children having OI using a quantitative method. Thus, this study provides valuable insight into the obscure concept of OHRQoL amongst this population. Furthermore, the results from this project will help clinicians to tailor their treatment plans to the needs of children with OI and prioritize them accordingly.

6.1.1 Summary of Oral findings

In the first attempt by Schwartz et al. in 1984 (87), investigated the oral manifestations of OI in 28 patients recruited from the Montreal Children's Hospital. They detected no significant difference in the DMFT ratio (caries index) among patients with different types of OI. Also, they reported an increase in the presence of a Class III malocclusion (66%) amongst patients having OI, with 100%

presence in OI type III. Furthermore, 63% of patients had a posterior crossbite, and 18% experienced a lateral/posterior openbite due to impacted first and second molars (Tables 6.7 and 6.8). This research was been conducted with the same population as that used in our study. The majority of our study participants were recruited from Montreal, and the aforementioned study (87) findings concur with the results of our study. However, the former study had a relatively small sample of 28 patients, with ages ranging between 2 and 45 years; it was conducted 34 years ago. Contrary to their (Schwartz et al.) observations on DI distribution amongst different OI types (same proportion of patients with types I and III have DI), the majority of patients in the present study with DI were classified as OI type III (64%). Furthermore, classifying patients based on their physical features (phenotype) will induce unresolvable issues like the subjective nature of OI type categorization and, ultimately, cause uncertainty and confusion. A summary of previous and present findings of the prevalence of DI and other outcomes related to orofacial characteristics of OI patients is being provided in table 6.7 and table 6.8, for better visualization and comprehension of the results.

In this study, we found that patients with OI type I have a higher number of teeth in comparison with OI type III ($p<0.05$). This is consistent with the findings of the research conducted in Sweden where the authors reported a high prevalence of tooth agenesis (17%) among general OI population with the higher rates in OI type III (47%) compared to OI type I (12%; $p=0.003$), and OI type IV (13%; $p=0.017$) (88). In an observational study on 64 black African individuals (3 months to 30 years of age) having OI III in South Africa (89), authors revealed the dominant presence of skeletal and dental class III malocclusion (41%) in this population. They further explained that an edge to edge bite was present in 25 % of cases and was identified only in primary dentition and mixed dentition period which potentially can progress to adult class III dental and skeletal malocclusion.

Furthermore, the authors reported an increased incidence of anterior and posterior cross-bites and anterior and posterior open-bites that was believed to be caused by high incidence of cl III malocclusion. These findings are in line with the results of our study as the prevalence of class III malocclusion, lateral open bite, and posterior crossbite is predominantly higher in OI type III both in children and teenagers with OI.

In chapter 33 of the book "Osteogenesis Imperfecta a translational approach to brittle bone disease," Retrouvey et al. have focused on the oral-facial aspect of OI (12). They have reported that although lateral open-bites are extremely rare (less than 1%) in a healthy population, it is overrepresented in the OI population with a prevalence of 27% amongst OI type III and up to 33% of type IV patients. They also noted, adult patients with cl III malocclusion and children with an edge to edge occlusion, which altogether account for 67% of their sample size, were mostly being found to have OI type III and IV. Moreover, authors stated that non-functional posterior lateral cross-bites were also a prevalent phenomenon observed in OI patients. The data obtained in their study are in good agreement with the findings in this study, but contrary to their observation, patients with posterior lateral open bites were mostly having OI type III (44% of children and 50% of adolescents. Another study carried out by Rizkallah J et al. also confirms the common occurrence of cl III malocclusion (57%) in OI population compared to healthy population (4%) and concluded that malocclusion in OI group was significantly more severe than healthy controls (using PAR and DR measures). Furthermore, patients affected by severe OI (type III) share common characteristics including severe malocclusions (class III) accompanied by anterior and posterior open bites and cross bites (11).

A descriptive study performed in Norway, recording the oral findings of 94 OI patients revealed an occurrence of DI in 19% and presence of mandibular overjet in 9.6% of the participants, being

lower than previous studies, yet higher than the healthy population. They reported OI patients have more missing teeth compared to healthy population, and that general oral health within OI population varies between OI types (27). The pattern and direction of findings from this research concur with our study; the difference is in the frequency of manifestation which is higher in our research. Worth mentioning, oral hygiene and caries status were not found to be significantly different between children and teenagers having different severity of the disease. This contrast could be caused by the difference in populations racial and geographical backgrounds, with the difference in their health care system reflecting on their oral hygiene. Furthermore, like some other researches above, this investigation has a case-control study design with the healthy population being the control group, compared to our cross-sectional study which inherently limits the extent of findings.

Table 6.7 – The prevalence of dentinogenesis imperfecta (DI) amongst patients with Osteogenesis imperfecta (OI), reported in earlier studies and the present study.

	Type I		**Type III**		**Type IV**		**Total**	
	OI n	DI n	OI n	DI n	OI n	DI n	OI n	DI (%)
Schwartz & Tsipouras (Canada-1984)(87)	20	8 (40%)	7	3 (43%)	1	1 (100%)	28	43
Lukinmaa (Finland-1987)(90)	45	4 (9%)	2	1 (50%)	16	13 (81%)	68	32
Lund et al. (Denmark-1998)(91)	50	4 (8 %)	16	13 (81%)	22	8 (37%)	88	28
O`Connell & Marini (NIH-1999)(92)	-	-	22	18 (82%)	18	11 (61%)	40	73
Malmgren & Nordgren (Sweden-2002)(93)	36	10 (28%)	15	10 (67%)	14	7 (50%)	65	42
Sæves et al. (Sweden-2009)(27)	74	7 (9.5%)	8	8 (100%)	12	2 (16.7%)	94	19
Majorana et al. (Italy-2010)(94)	9	4 (45%)	3	3 (100%)	4	3 (75%)	16	63
Present study (Canada/US-2017)	65	9 (14%)	30	19 (64%)	34	17 (50%)	129	35

Table 6.8- Summary of orofacial findings of OI, reported in earlier studies and in the present study.

	Other findings
Schwartz & Tsipouras (Canada-1984)(87)	• Class III malocclusion in 67 % of the cohort (100% in OI Type III group) • Presence of posterior crossbites in 63% of patients. • Impacted first or second molars (primary and permanent) in 5 patients (18%) • History of tooth fracture in 22% of patients. • Attrition of teeth was present in 11% of subjects. • DMFT ratio increased by age irrespective of DI status of patients. • Patients with OI type III and DI had a higher DMFT ratio (50%) than patients without DI (37%).
Lukinmaa (Finland-1987)(90)	• Tooth histological finding: irregularity of dentin matrix and tubular pattern in the circumpulpal dentin and normal mantle dentin were observed.
Lund et al. (Denmark-1998)(91)	• Denticles, i.e., calcifications within the pulpal cavity, were found more frequently in OI patients than in control individuals.
O`Connell & Marini (NIH-1999)(92)	• All findings are among 40 children having types III and IV. • Class III malocclusion in 77% of patients. • High incidence of anterior (25%) and posterior (31%) open bites. • High incidence of anterior (28%) and posterior (42%) crossbites. • A delay in dental development was observed in 21% of patients type III OI. • Ectopic eruption occurred in 33% of patients.
Malmgren & Nordgren (Sweden-2002)(93)	• Presence of agenesis in 23% of patients. • Appically extended pulp chambers observed in 42% of patients. • Impacted second permanent molars in 37% of patients were evident.
Waltimo-Sirén et al. (Finland-2005)(95)	• Growth discrepancies most prominently affected the vertical jaw dimensions resulting in relative mandibular prognathism. • OI may affect the location of all reliable cephalometric landmarks, confounding normal analysis.
Sæves et al. (Sweden-2009)(27)	• Persons with OI have more missing teeth compared with the general population. • Mandibular overjet was present in 9.6%. • The general oral health within the population with OI varies between individuals with mild OI and those with more severe OI.
Majorana et al. (Italy-2010)(94)	• There is no correlation between the type of OI and the type of discoloration.
Present study (Canada/US-2017)	• Class III malocclusion in 51 % of patients which proportionally speaking the majority have OI type III. • Posterior crossbites presented in 36% of patients and were more common in OI type III. • In 29% of patients, a lateral/posterior open bite was observed in patients with proportionally being more frequent amongst OI type III.

6.1.2 Summary of OHRQoL findings

Focusing on the primary aim of the study, this thesis to our knowledge is the first study to investigate the OHRQoL and its associations with orofacial traits of OI amongst children and adolescents employing a quantitative method. Our results disclose for the first time the strong negative association between a posterior crossbite and the overall profile of OHRQoL due to functional limitation. Adolescents with any type of OI having posterior crossbite had a more negative overall profile of OHRQoL when compared to those not having a posterior crossbite.

Children and adolescents with OI have lower scores in the physical domain of HRQoL but yet share psychosocial QoL scores equivalent to the healthy population (14, 96). Lower aerobic capacity, impaired bone development together with the fear of fracture leads to lower physical fitness and deteriorated physical QoL compared to peers without OI (5, 97). However, OI patients manage to maintain their psychosocial QoL by developing coping strategies, redefining life within the realm of possibilities and their physical constraints and creating a "new normal" life (5, 65). Moreover, according to self-report and parent-report (proxy evaluation), children with OI types III and IV report worse physical QoL but similar mental QoL when compared to patients with OI type I (37, 82, 83). The findings on OI patients' HRQoL remains valid for their OHRQoL. The latter sentence reaffirms the fact that one cannot separate mouth from the rest of the body and assess OHRQoL independently. Although teenagers with OI type III and IV in our study exhibited a significantly higher levels of oral functional limitations, they shared relatively similar scores in other three domain (OS, EWB, SWB) as well as total CPQ scores. Although not statistically significant, adolescents having OI type III and IV have 4.11 (95% CI: 0.76- 21.98) and 2.67 (95% CI: 0.82- 8.71, respectively) times higher odds of experiencing lower OHRQoL compared to OI type I. Similar pattern of findings was found in children with OI (Table 5-2) but it is not conclusive since it is not statistically significant. After adjusting for confounding the effect of variables in the

regression model, posterior crossbite significantly deteriorates teenagers' perception about their OHRQoL. Teenagers with posterior crossbite compare to those without, have 5.92 (95% CI: 1.67-20.91) times higher odds of suffering from lower grades of OHRQoL in general.

To date, numerous studies have evaluated HRQoL in various settings employing quantitative, qualitative, and mixed methods approach, yet no research has investigated OHRQoL of OI patients. In a recently published integrative review paper by Nghiem et al. (4), the pain experienced by children and adolescents having OI have been comprehensively reviewd and explained. Pain is described to be a commonly experienced symptom for children and adolescents diagnosed with OI, and despite several differences in methods assessing pain, all agree upon the presence of it. Pain experienced by children and adolescents can be both acute (fracture pain) and chronic (non-fracture pain). By the intensity of pain reported from patients, spinal pain (scoliosis) is known to be the most painful experience with fracture pain being second, and non-fracture pain come third. Children and adolescents most often used the words "uncomfortable" or "throbbing" to describe their fracture pain, whereas words such as "annoying" and "aching" were used to describe their nonfracture pain. On average, the pain was found to be experienced in almost three days per week and 24 days per month in their review (4, 38). They have also explained how pain can alter and interfere with many aspects of children's daily lives and cause mobility restriction, sleep disturbances, and decrease involvement in self-care, traveling, school, work and participating in leisurely activities. Furthermore, they have categorized pain management techniques to pharmacologic (analgesics) and nonpharmacologic interventions. Seeking for social support, positive self-statements, and behavioral or cognitive distraction to be nonpharmacologic pain-coping techniques utilized by children and adolescents with OI (4). Pain is the main concern of "Oral Symptom" domain of CPQ questionnaire. No study has explored and contrasted the amount of pain between different OI types, but abundant research exists comparing pain level of OI

patients and healthy individuals. Nevertheless, the results from our study reveals; although not statistically significant but children with OI type III and IV have 1.16 (95%CI; 0.28- 4.73) and 0.55 (95%CI; 0.13- 2.45) times higher odds to have higher grades (worsen) of oral symptoms compared to OI type I. Also, having OI type III (OR: 0.71; 95% CI: 0.13- 3.79) and IV (OR: 1.18; 95% CI: 0.38- 3.64) were associated with a higher grade of oral symptoms score (CPQ subscale) amongst adolescents when compared to OI type I. Noteworthy, the results on teenagers with OI type III compared to type I is counterintuitive since one may expect OI type III patients to have higher odds of worse oral symptoms when compared with OI type I. This can be explained by the fact that the oral traits of the disease, have been included in the final model and due to their inherent correlation with OI types, they can potentially draw and diffuse the effect from OI types to oral characteristics of the disease. OI teenagers with posterior crossbite compared to those without, have 5.14 (95% CI: 1.45- 18.15) times higher odds to suffer from their oral symptoms. Presence of DI, although not statistically significant, plays as a contributing factor hindering oral symptoms domain of CPQ scale (OR:1.13; 95%CI: 0.37- 3.47). Unlike a teenage group, class III malocclusion is the major factor contributes to the impaired experience of an oral symptom in children with OI (OR:4.62; 95% CI: 1.11- 19.32) and similar to adolescents DI is the second major element (although not significant). One must be aware of wide confidence intervals attained in this study which is a direct result of low sample size together with a high number of variables adjusted for in the regression model.

Other than pain, children with OI described how their extensive fear of fractures and situations that may cause a fracture holds them back from undertaking certain activities (functional limitation), consequently resulting in diminished vitality, social functioning ability and social interactions (social well-being) with a reduced mental health and emotional functioning (emotional well-being) (6, 64, 98). No study has evaluated oral functional limitation resulting from the

orofacial condition and manifestation of OI. The results from our research shows teenagers with OI type III and Type IV have 7.3 (95% CI: 1.2- 43.8) and 5.5 (95% CI: 1.57- 19.55) times higher odds to have higher levels (worsen) of functional limitations compared to OI type I with non-functional posterior crossbite being the main significant contributing factor. Teenagers with any type of OI having posterior crossbite experience higher grades of functional limitations (OR: 6.13; 95% CI: 1.67- 22.58) compared to those not having a posterior cross bit. Although not statistically significant, along with posterior crossbite, having lateral open bite associated with higher scores of functional limitations (OR:1.91; 95% CI: 0.58- 6.22). The latter finding verifies that it is a combination of lateral open bite and posterior crossbite (non- functional posterior crossbite) that results in having statistically significantly lower oral-related function amongst teenagers having any type of OI. The same pattern of findings were observed amongst children but without statistical significance that can be explained by the lower sample size in children group.

Additionally, restrictions imposed by the means of transportations like canes, crutches, or wheelchairs on OI patients is a significant factor negatively contributing to their functional and social well-being (6, 99). Other than their physical limitations, people's perception of their disability pushes them even further to be left out of activities with their healthy peers (83). Nonetheless, studies have shown that OI patients with varying OI severities had similar happiness scores and emotional, functional capacities as healthy individuals. Doing so by employing coping techniques like, adopting a positive mindset (optimistic view), and using humor in their daily life. However, life satisfaction and depression scores were found to considerably vary in OI patients, indicating difficulties they have coping with their everyday realities. The obtained scores for emotional well-being (EWB) subscale of OHRQoL amongst teenagers, despite not having statistical significance, suggests lower levels of EWB amongst OI types III (5.7 ± 5.9) and IV (5.5 ± 6.9) compared to OI type I (3.6 ± 5.7) (Table 5.4). After adjusting for the potential confounders

in the model, adolescents with OI type III and IV still display to have higher odds of experiencing lower levels of EWB by factors of 2.87 (95% CI: 0.53- 15.37) and 2.18 (95% CI: 0.65- 7.34), respectively, when compared to OI type I ($p>0.05$; table 5.6). Posterior crossbite found to be significantly associated with the EWB of teenagers having any type of OI. Adolescents with posterior crossbite have 4.71 (95% CI: 1.37- 16.08) times higher odds of feeling emotional despair compared to those without posterior crossbites (table 5.6). Findings from children group were not conclusive since they did not have statistical significance (table 5.5).

Studies exploring social relationships of OI patients have explained children's good social skills in forming friendships with their healthy peers and revealed that the severity of OI might act as a barrier to children's ability to establish social or romantic relationships. They found that adolescents with OI type III compared to type I and IV demonstrate a decreased ability to construct close friendships, as well as a lower perceived romantic appeal (82, 100). One study has reported a significant reduction in social functioning of children with OI type III and IV compared to OI type I when evaluated by the parents (82). Based on our study, findings from recent mentioned studies cannot be explained by the oral condition of these patients since both in children, and adolescents SWB (CPQ subscale) are somewhat similar among different OI types (tables 5.5 and 5.6).

6.2 Limitations

6.2.1 Methodological limitations

The CPQ questionnaire is a generic instrument that has been used in five different types of studies:

1. Evaluating the associations between oral conditions and OHRQoL in healthy population (e.g., disparities in OHRQoL (101), evaluation of OHRQoL in general child population (102); cross-sectional studies).

2. Investigating the impact of an intervention on OHRQoL (e.g., longitudinal evaluation of the impact of dental caries treatment on OHRQoL (103); clinical trials).
3. Exploring changes in OHRQoL over time without any intervention (e.g., dental appearance and educational transition (104), determinants of OHRQoL over time (105); longitudinal studies).
4. Assessing OHRQoL in patients suffering from a condition, disease or disorder in comparison with healthy population (e.g., Sickle cell disease (57), undergone cancer therapy(56), psychiatric inpatients (106), tooth agenesis (107); case-control studies).
5. Evaluating OHRQoL amongst patients with a specific health condition and investigating the determinants of it (e.g., AIDS (108); cross-sectional).

   The latter mentioned type is closely similar to our study as we are assessing OHRQoL amongst OI patients without a control group as well as investigating the extent of association between oral and craniofacial conditions (both general and disease-related) with OHRQoL. Using CPQ questionnaire as an OHRQoL measurement in children having OI is subject to criticism since it is a generic instrument and might not be appropriate to assess OHRQoL and its associations with disease-related manifestations of OI without having a control group (healthy population).

Furthermore, floor effect (i.e., no impact) has been observed in our study (tables 5.2 and 5.4). Having floor effect in the results suggests either there are no issues in that specific domain amongst that population (highly unlikely), or the instrument does not have discriminatory power to capture those issues (lack of appropriateness) or the questionnaire is lacking precision (accuracy of distinction) in measurements. In either case, having floor effect in a cross-sectional evaluation will undoubtedly result in failure in measuring meaningful changes in health in an interventional study (i.e., clinical trials; lack of responsiveness). In summary, having ‘floor effect’ raises concern

mainly in three scopes of instrument selection and its application namely in ‘appropriateness,’ ‘precision,’ and ‘acceptability’ of the measure.

Appropriateness is the extent to which instrument content is suitable to the specific application. One of the broad objectives of any Patients Reported Outcome Measures (PROMs) is to have discrimination power. “Discrimination is concerned with the measurement of differences between patients when there is no external criterion available to validate the instrument” (e.g., EWB and SWB in OI patients)(109). The results from our study have shown no difference between EWB and SWB domains of children and adolescents having OI with different severity. This can be partially explained by CPQ not being an appropriate instrument to capture the real impact of disease-related conditions on EWB and SWB of patients. Worth mentioning, since being a generic instrument, it can be an appropriate option for case-control evaluations, comparing OI patients with healthy individuals. However, since it does not tap (capture) sign and symptoms prevalent or relevant amongst OI patients, it may not be the most suitable measure to evaluate OHRQoL amongst different types of OI. In conclusion, the outcome of the present study does not have as much clinical relevance as a hypothetical study employing disease-specific questionnaire.

Precision concerns the distinction made by the instrument and addresses number of issues related to methods of scaling and scoring items and their distribution over the range of the construct being measured. End effect happens when a large proportion of respondents score at the floor or ceiling of the score distribution. It’s been considered as an indicator that the instrument may be measuring a confined range of a construct which can weaken both discriminatory power and responsiveness of the measure (110).

Acceptability is the extent to which an instrument is acceptable to patients. To be acceptable, there is a number of factors that should be taken into account like the questionnaire design, health status

of the respondent, language of the respondent, mode of administration, etc. Most importantly, instruments having clear relevance to patients' specific health condition is deemed to have higher acceptability. The latter statement reaffirms the importance of developing disease-specific measures.

Assuming that another study aims to compare the health status scores of patients with a specific disease to those of general population, then a disease-specific instrument is not an appropriate measuring option as the healthy community does not experience same health issues as the diseased patients. The recent comment highlights the appropriateness of CPQ questionnaire usage in case-control studies.

All above mentioned underlines the importance of developing a disease-specific instrument to assess OHRQoL amongst OI patients. Nevertheless, since CPQ questionnaire is the only measure designed to capture children's perception of their OHRQoL and given that a disease-specific instrument has not yet been developed for patients having OI, for the lack of any better option we employed CPQ for our study. Recently, new steps were taken to develop a disease-specific HRQoL that is currently under process (83) but yet there is a long way before development of OI-specific OHRQoL measure.

6.2.2 categorizing patient into different OI types

As mentioned before, the lack of clear and objective criterion in classifying patients of different severity into OI types I to IV raises confusion and uncertainty. Majority of the problem is caused by the patients with moderate OI (type IV), as some may erroneously group them with mild OI (type I) and others consider it to be more severe and hence coupled with OI type III. This denotes the need to use a consistent classification system between centers. Moving forward, it is a necessity to adopt a new classification system based on genotype rather than phenotype.

6.2.3 Recruitment/ selection bias

The hospital/clinic-based recruitment method used in this study may generate recruitment/selection bias since it may have oversampled more severely affected patients as they are more likely to seek medical care from a specialized clinic than less severely affected individuals. To limit recruitment bias, one strategy may be to identify potential participants directly from the general population (population-based studies) to randomly reach a spectrum of subjects having the disease with different severity in a given geographic region (5). However, expert experience has shown that the great majority, if not all, children with OI are followed in a hospital setting, thus the risk for selection bias from a hospital setting should be very small.

6.2.4 Bias due to confounding

Potential confounders for the analysis, in absence of prior knowledge, were identified employing a theoretical framework (figure 4.1) to draw the association between exposure, outcome and other variables in the study. Minimum set of potential confounders were then selected by STATA (statistical software package) using block-wise selection methods. We believe that these procedures increase the strength of our study since it's been grounded in theoretical understanding of the variables in the study and their association with each other. Also, appropriately choosing and later on controlling for the confounding factors will restrict residual confounding effect to a minimum leading to a more robust and reliable findings.

6.2.5 Sample size limitations

Similar to other surveys on OI patients, this study may have been constrained by small sample size. This study is part of a larger ongoing multicentral cohort study with the aim of understanding the natural history of OI; the data set used here is a subsection of the full collected data. We narrowed the inclusion criteria to patients aged between 8 to 10 (CPQ_{8-10}) and 11 to 14 (CPQ_{11-14}) years old. We ended up having 56 children and 82 adolescents in our study which is considered to

be a relatively small sample size for rigorous statistical analyses. However, given the rarity of OI disease, this is a reasonable sample size (being plausible to recruit) and, to the best of our knowledge, this was the largest sample size ever enrolled in any study on OI patients.

6.2.6 Generalizability

Results from hospital-based cross-sectional studies in comparison with population-based studies possess lower generalizability. We have adopted every possible measure to reduce non-participation rate (we had 100% participation) and therefore increasing the sample size and representativeness. However, given the multicentral nature of this study (patients having different cultural backgrounds) and the fact that it is the largest sample ever recruited on children with OI, we believe that results of our study have adequate generalizability and provides a comprehensive understanding of the factors that might affect OHRQoL in children having OI.

6.3 Implications

6.3.1 Clinical Implications

The results from this study will provide clinicians and health-care professionals with a better understanding of OHRQoL in OI patients. Furthermore, it will assist them to identify individuals most at risk for having a low OHRQoL and tailor interventions aimed at enhancing OHRQoL in children and adolescents having OI.

6.3.2 Implications for future research

Although this study provides valuable information about OHRQoL in OI population, studies including larger sample size may contribute to establishing more accurate findings. Furthermore, any detected differences in perception of OHRQoL between OI patients and individuals with no health condition (case-control study design) could provide evidence, helping to bridge the gap in the literature and give us a better understanding of OHRQoL status in OI patients in contrast to a

healthy population. Moreover, conducting an interventional clinical trial study will further confirm the findings of this study by evaluating OHRQoL at the baseline and after treating patients' posterior crossbites.

Also, as mentioned previously, to address the issues (e.g., end effect) of using generic questionnaires to evaluate OHRQoL, extensive attention should be paid to develop a disease-specific instrument which is of utmost importance in collecting reliable, relevant, and more specific data.

Children with disabilities have a different appraisal of their QoL compared to their parents (111). Thus, whenever possible, QoL evaluation should include both children and parents (legal guardian, care giver) perspective to inform clinical practice and research.

7. Conclusion

Posterior crossbites amongst teenagers with OI is associated with higher levels of oral symptoms (OR), functional limitations (FL), and emotional well-being (EWB) resulting in significantly lower OHRQoL scores. Thus, clinicians can use this information to prioritize their treatment plans in teenagers with OI.

8. Reference

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9. APPENDIX I

Baseline medical assessment, family history and demographics questionnaires

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Baseline Assessment Form

Local ID:	_____	Participant ID:	_____
Site:	_____	Date of Visit:	_____
Interviewer User ID:	_____		

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Baseline Assessment Review:

Subtype of OI: O I O II O II/III O III O IV O V O VI O VII O VIII

Prenatal

OI suspected antenatally: O Yes O No O Unknown

If yes: O Family History O Ultrasound

Intrauterine Growth Retardation (IUGR): O Yes O No O Unknown

In utero fractures: O Yes O No O Unknown

If yes: □ Long Bones □ Ribs □ Skull

Source of information:

O Parent/Subject recollection.

O Medical records review.

Labor and Delivery

Gestation: ____ weeks O Unknown

Source of information:

O Parent/Subject recollection.

O Medical records review.

Presentation: O Breech O Vertex O Unknown

Source of information:

○ Parent/Subject recollection. ○ Medical records review.
Mode of Delivery: ○ Spontaneous Vaginal Delivery (SVD) ○ Induced Vaginal Delivery (IVD) ○ Cesarean section ○ Unknown If Cesarean section: Mode: ○ Classic ○ Low Reason: ○ Elective – maternal reasons ○ Elective – fetal reasons ○ Emergent Source of information: ○ Parent/Subject recollection. ○ Medical records review.
Birth weight: ____ grams ○ Unknown Source of information: ○ Parent/Subject recollection. ○ Medical records review
Length: ____ cm ○ Unknown Source of information: ○ Parent/Subject recollection. ○ Medical records review
OFC (Occipitofrontal head circumference): ____ cm ○ Unknown Source of information: ○ Parent/Subject recollection. ○ Medical records review.
Length of baby's hospital stay at birth: ○ ≤ 3days ○ 4 – 7 days ○ 1 – 2 weeks ○ > 2 weeks

O Unknown

Source of information:

O Parent/Subject recollection.

O Medical records review.

Fractures at birth: O Yes O No O Unknown

If yes: Long bone fractures O Yes O No #:_____

Rib fractures O Yes O No #:_____

Clavicle fracture O Yes O No

Skull fracture O Yes O No

Source of information:

O Parent/Subject recollection.

O Medical records review.

Diagnosis

Clinical: O Yes O No

If yes: O Family History O Radiographs O Exam

If Radiographs: □ Fractures □ Wormian Bones □ Osteopenia

Source of information:

O Parent/Subject recollection.

O Medical records review.

DNA Mutation Identified in Participant: O Yes O No

Source of information:

O Parent/Subject recollection.

O Medical records review.

DNA Mutation Identified in Family Member: O Yes O No

If yes, Family Member?

O Mother

O Father

○ Son ○ Daughter ○ Sibling ○ Cousin ○ Mother's sibling ○ Father's sibling ○ Maternal grandparent ○ Paternal grandparent ○ Other: _____ Source of information: ○ Parent/Subject recollection. ○ Medical records review.
Collagen Electrophoresis: ○ Yes ○ No If yes: ○ Quantitative Defect ○ Qualitative Defect Source of information: ○ Parent/Subject recollection. ○ Medical records review.

Name of Person Completing Form: _____

Signature of Person Completing Form: _____ Date: _____

Family History and Linkage Data

Protocol Number:	_____	Participant ID:	_____
Site:	_____	Date of Visit:	_____
Interviewer User ID:	_____		

Family History:

Family history of OI: ○ Yes ○ No ○ Unknown

If yes: ○ Mother ○ Father ○ Sibling ○ Other: _____

Maternal Height: _____ cm ○ unknown

Paternal Height: _____ cm ○ unknown

Consanguinity: ○ Yes ○ No ○ Unknown

Family Linkage Data

Is any member of participant's family enrolled in study? ○ Yes ○ No

If yes:

1. Please provide family member's BBD 7701 study IDs:
   Participant ID: _____

   Local ID: _____

   Family member's relationship to the participant:

   ○ Mother

   ○ Father

   ○ Son

   ○ Daughter

   ○ Sibling

   ○ Cousin

   ○ Mother's sibling

   ○ Father's sibling

   ○ Maternal grandparent

- ○ Paternal grandparent
- ○ Other: _____

2. Please provide family member's BBD 7701 study IDs:
   Participant ID: _____

   Local ID: _____

   Family member's relationship to the participant:

   - ○ Mother
   - ○ Father
   - ○ Son
   - ○ Daughter
   - ○ Sibling
   - ○ Cousin
   - ○ Mother's sibling
   - ○ Father's sibling
   - ○ Maternal grandparent
   - ○ Paternal grandparent
   - ○ Other: _____

Add Additional Family Members

Name of Person Completing Form: _____

Signature of Person Completing Form: _____ Date: _____

Demographics

Protocol Number:	_____	Participant ID:	_____
Site:	_____	Date of Visit:	_____
Interviewer User ID:	_____		

1. Participant Age (either Date of Birth or Age is required, use Date of Birth **unless** disallowed by your local institution's IRB):

Date of birth: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR) **OR**

Age at registration: _____ years OR _____ month

2. Gender: ○ Male ○ Female

3. Ethnicity (*select one):*

○ Hispanic, Latino or Spanish Origin
○ Not Hispanic, Latino, or Spanish Origin
○ Unknown or not reported
○ Refused

4. Race *(check all that apply):*

☐ American Indian or Alaska Native
☐ Asian
☐ Black or African American
☐ Native Hawaiian or Other Pacific Islander
☐ White
☐ Refused
☐ Unknown

Name of Person Completing Form: _____

Signature of Person Completing Form: _____ Date: _____

10. APPENDIX II:

Dental Clinical Examination

Brittle BONE DISORDERS CONSORTIUM

BBD 7701: *Longitudinal Study of OI*

Dental Clinical Examination Form

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Local ID:	_____	Participant ID:	_____
Site:	_____	Date of Visit:	_____
Interviewer User ID:	_____		

1. Dental Examination

	Upper Right							Upper Left						
Permanent tooth	7	6	5	4	3	2	1	1	2	3	4	5	6	7
Primary tooth			5	4	3	2	1	1	2	3	4	5		
Present (1) Missing (0)														
Caries (0 or 1)														
Filled (0 or 1)														
Ectopic (0 or 1)														
	Lower Right							Lower Left						
Permanent tooth	7	6	5	4	3	2	1	1	2	3	4	5	6	7
Primary tooth			5	4	3	2	1	1	2	3	4	5		
Present (1) Missing (0)														
Caries (0 or 1)														
Filled (0 or 1)														
Ectopic (0 or 1)														
Color of Dentition	❑ Normal with no evidence of dentinogenesis imperfecta ❑ Opalescent / Blue gray discoloration ❑ Yellow / Brown discoloration													

2. Dental hygiene assessment

Age	Tooth Surface					
4 to 6		UR4 Li	UR 1 B	LoLe1 Li	LoLe5 Li	
7 to 10	UR 4 B	ULe 1 B	ULe 6 B	LoLe 5 Li	LoR 2 B	LoR 6 Li
11 and older	UR 6 B	UR 1 B	ULe 6 B	LoLe 6 Li	LoLe 1 B	LoR 6 Li

U = Upper Lo= lower R= right Le= Left B = Buccal Li= Lingual

3. Occlusion

Molar Classification: Right side

- ❑ Class I
- ❑ Class II
- ❑ Class III
- ❑ Cannot determine

Molar Classification: Left side

- ❑ Class I
- ❑ Class II
- ❑ Class III
- ❑ Cannot determine

If patient is in primary dentition, a flat terminal plane is considered Class I molar, a distal step is Class II and a mesial step is Class III

Canine Classification: Right side

- ❑ Class I
- ❑ Class II
- ❑ Class III
- ❑ Cannot determine

Canine Classification: Left side

- ❑ Class I
- ❑ Class II
- ❑ Class III
- ❑ Cannot determine

Overbite ❑ 0% ❑ 10% ❑ 25% ❑ 50% ❑ 75% ❑ 100%

Openbite ❑ yes ❑ no

Lateral Openbite ❑ No ❑ 1mm ❑ 3mm ❑ over 3mm

Overjet ❑ Negative ❑ Positive ❑ Edge to edge

Dental Midline Deviation ❑ Yes ❑ No

Upper midline: Deviated ❑ 1mm ❑ 3mm ❑ over 3mm

Lower midline: Deviated ❑ 1mm ❑ 3mm ❑ over 3mm

Posterior Crossbite ❑ yes ❑ no

Anterior Crossbite ❑ yes ❑ no

Name of Person Completing Form:

Signature of Person Completing Form: _____ Date: _____

11. APPENDIX III:

Child Perceptions Questionnaire 8-10 (CPQ_{8-10})

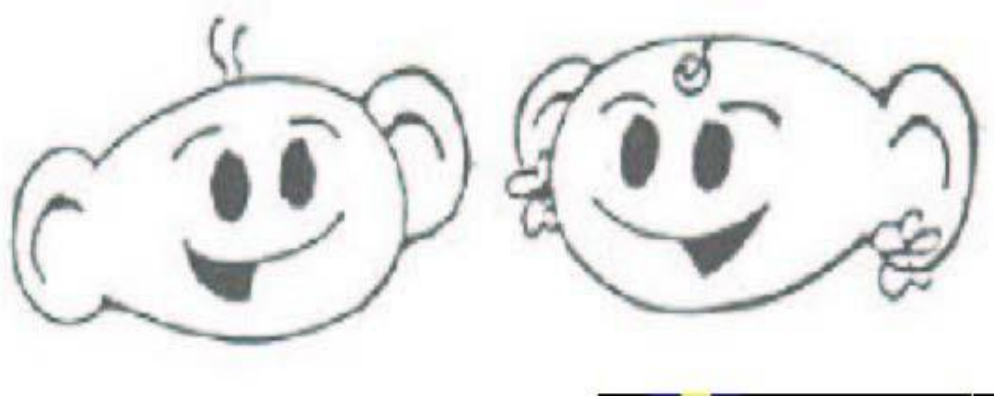
ORAL HEALTH RELATED QUALITY OF LIFE QUESTIONNAIRE

8-10 years

We are doing this study to understand better things that may happen to children because of their **teeth and mouth**.

PLEASE REMEMBER:

- Don't write your name on the questionnaire.
- This is **not a test** and there are no right or wrong answers.
- Answer as **honestly** as you can.
- **Don't talk to anyone** about the questions when you are answering them.
- **No one** you know will see your answers.
- Read each question **carefully** and think about the things that have happened to you in the **past 4 weeks** .
- Before you answer, ask yourself: **"Does this happen to me because of my teeth or mouth?"**



- Put an x in the box for the answer that is best for you.

Today's date:_____/_____/_____

DAY MONTH YEAR

FIRST, A FEW QUESTIONS ABOUT YOU

1. When you think about your teeth or mouth, would you say that they are:

- ❑ Very good
- ❑ Good
- ❑ O.K
- ❑ Poor

2. How much do your teeth or mouth bother you in your everyday life?

- ❑ Not at all
- ❑ A little bit
- ❑ Some
- ❑ A lot

NOW A FEW QUESTIONS ABOUT YOUR TEETH AND MOUTH

How often have you had:

3. Pain in your teeth or mouth in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

4. Sore spots in your mouth in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

5. Pain in your teeth when you drink cold drinks or eat hot foods in the past 4 weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

6. Food stuck in your teeth in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

7. Bad breath in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

How often have you:

8. Needed longer time than others to eat your meal because of your teeth or mouth in the past 4 weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

9. Had a hard time biting or chewing food like apples, corn on the cob or steak because of your teeth or mouth in the past 4 weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

10. Had trouble eating foods you would like to eat because of your teeth or mouth in the past 4 weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

11. Had trouble saying some words because of your teeth or mouth in the past 4 weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

12. Had a problem sleeping at night because of your teeth or mouth in the past 4 weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

QUESTIONS ABOUT FEELINGS

How often have you:

13. Been upset because of your teeth or mouth in the past 4 weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

14. Felt frustrated because of your teeth or mouth in the past 4 weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

15. Been shy because of your teeth or mouth in the past four weeks?

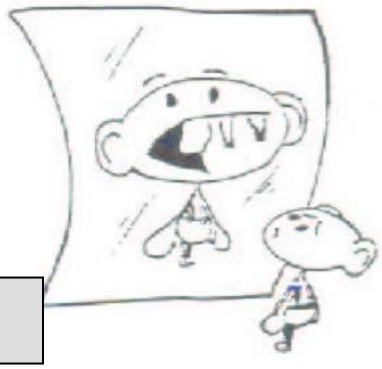
- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

16. Been concerned what other people think about your teeth or mouth in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

17. Worried that you are not as good-looking as others because of your teeth or mouth in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday



QUESTIONS ABOUT YOUR SCHOOL

How often have you:

18. Missed school because of your teeth or mouth in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

19. Had a hard time doing your homework because of your teeth or mouth in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

20. Had a hard time paying attention in school because of your teeth or mouth in the past 4 weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

21. Not wanted to speak or read out loud in class because of your teeth or mouth in the past 4 weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

QUESTIONS ABOUT YOU BEING WITH OTHER PEOPLE

How often have you:

22. Stayed away from activities like sports and clubs because of your teeth or mouth in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

23. Not wanted to talk to other children because of your teeth or mouth in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

24. Tried not to smile or laugh when with other children because of your teeth or mouth in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

25. Not wanted to be with other children because of your teeth or mouth in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

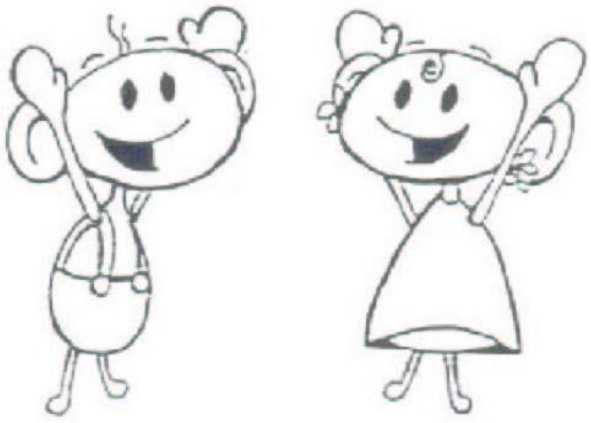
How often have:

26. Other children teased you or called you names because of your teeth or mouth in the past 4 weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday

27. Other children asked you questions about your teeth or mouth in the past four weeks?

- ❑ Never
- ❑ Once or twice
- ❑ Sometimes
- ❑ Often
- ❑ Everyday or almost everyday



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THANK YOU FOR
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12. APPENDIX IV

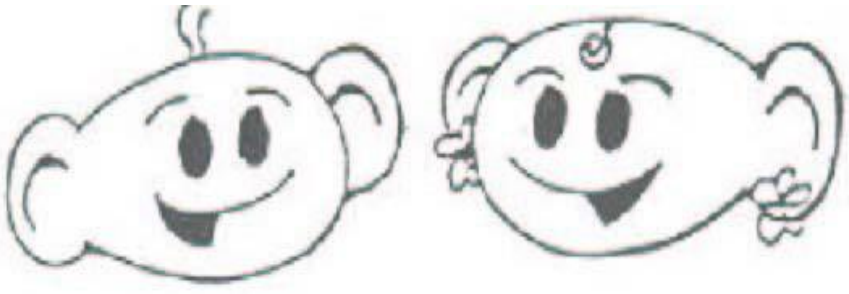
Child Perceptions Questionnaire 11-14 (CPQ_{11-14})

ORAL HEALTH RELATED QUALITY OF LIFE QUESTIONNAIRE

This questionnaire will help us better understand problems children may have with their teeth, mouth, lips and jaws. By answering the questions, you will help us learn more about young people's experiences.

PLEASE REMEMBER:

- Don't write your name on the questionnaire.
- This is **not a test** and there are no right or wrong answers.
- Answer as **honestly** as you can. Don't talk to anyone about the questions when you are answering them. Your answers are **private**; no one you know will see them.
- Read each question **carefully** and think about your experiences in the **past 3 months** when you answer.
- Before you answer, ask yourself**: "Does this happen to me because of problems with my teeth, lips, mouth or jaws?"**
- Put an x in the box for the answer that is best for you.



Today's date:_____/_____/_____
DAY MONTH YEAR

FIRST, A FEW QUESTIONS ABOUT YOU

1. Would you say the health of your teeth, lips, jaws and mouth is:
   - ❑ Excellent
   - ❑ Very good
   - ❑ Good
   - ❑ Fair
   - ❑ Poor

2. How much does the condition of your teeth, lips, jaws or mouth affect your life overall?
   - ❑ Not at all
   - ❑ Very little
   - ❑ Some
   - ❑ A lot
   - ❑ Very much

QUESTIONS ABOUT ORAL PROBLEMS

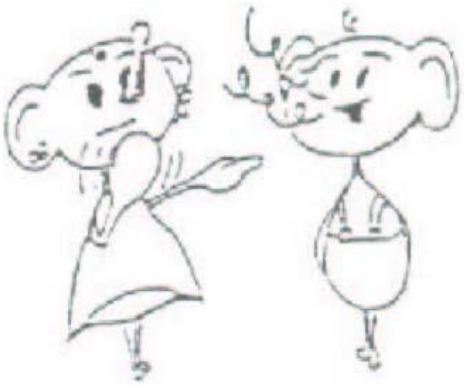
In the past 3 months, how often have you had:

3. Pain in your teeth, lips, jaws or mouth?
   - ❑ Never
   - ❑ Once or twice
   - ❑ Sometimes
   - ❑ Often
   - ❑ Everyday or almost every day

4. Bleeding gums?
   - ❑ Never
   - ❑ Once or twice
   - ❑ Sometimes
   - ❑ Often
   - ❑ Everyday or almost everyday

5. Sores in your mouth?
   - ❑ Never
   - ❑ Once or twice
   - ❑ Sometimes
   - ❑ Often
   - ❑ Everyday or almost everyday

6. Bad breath?
   - ❑ Never
   - ❑ Once or twice
   - ❑ Sometimes
   - ❑ Often
   - ❑ Everyday or almost everyday



7. Food stuck in or between your teeth?
   - ❑ Never
   - ❑ Once or twice
   - ❑ Sometimes
   - ❑ Often
   - ❑ Everyday or almost everyday

8. Food stuck in the top of your mouth?
   - ❑ Never
   - ❑ Once or twice
   - ❑ Sometimes
   - ❑ Often
   - ❑ Everyday or almost everyday

For the next questions…
Has this happened because of your <u>teeth, lips, jaws or mouth?</u>
In the past <u>3 months</u>, how often have you had:

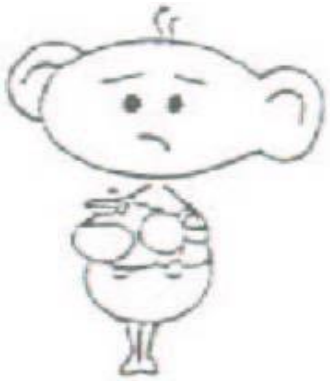
9. Breathed through your mouth?
   - ❑ Never
   - ❑ Once or twice
   - ❑ Sometimes
   - ❑ Often
   - ❑ Everyday or almost everyday

10. Taken longer than others to eat a meal?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

11. Everyday or almost everyday Had trouble sleeping?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

In the past 3 months, because of your teeth, lips, mouth or jaws how often has it been:

12. Difficult to bite or chew food like apples, corn on the cob or steak?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday



13. Difficult to open your mouth wide?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

14. Difficult to say any words?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

15. Difficult to eat foods you would like to eat?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

16. Difficult to drink with a straw?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

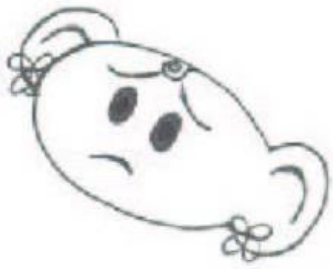
17. Difficult to drink or eat hot or cold foods?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

QUESTIONS ABOUT FEELINGS

Have you had the feeling because of your teeth, lips, jaws or mouth? If you felt this way for another reason, answer 'Never'.
In the past <u>3 months</u>, how often have you:

18. Felt irritable or frustrated?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

19. Felt unsure of yourself?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

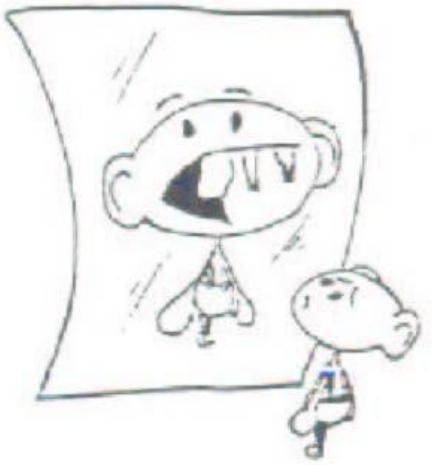


20. Felt shy or embarrassed?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

In the past 3 months, because of your teeth, lips, mouth or jaws, how often have you:

21. Been concerned what other people think about your teeth, lips, mouth or jaws?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

22. Worried that you are not as good-looking as others?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday



23. Been upset?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

24. Felt nervous or afraid?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

25. Worried that you are not as healthy as others?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

26. Worried that you are different than other people?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

QUESTIONS ABOUT SCHOOL

Have you had these experiences because of your <u>teeth, lips, jaws or mouth</u>? If it was for <u>another reason</u>, answer 'Never'.

In the past <u>3 months</u>, how often have you:

27. Missed school because of pain, appointments, or surgery?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

28. Had a hard time paying attention in school?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

29. Had difficulty doing your homework?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

30. Not wanted to speak or read out loud in class?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

QUESTIONS ABOUT YOUR SPARE-TIME ACTIVITIES & BEING WITH OTHER PEOPLE

Have you had these experiences because of your <u>teeth, lips, jaws or mouth</u>? If it was for <u>another reason</u>, answer 'Never'.
In the past <u>3 months</u>, how often have you:

31. Avoided taking part in activities like sports, clubs, drama, music, school trips?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

32. Not wanted to talk to other children?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

33. Avoided smiling or laughing when around other children?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

34. Had difficulty playing a musical instrument such as a recorder, flute, clarinet, trumpet?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

35. Not wanted to spend time with other children?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

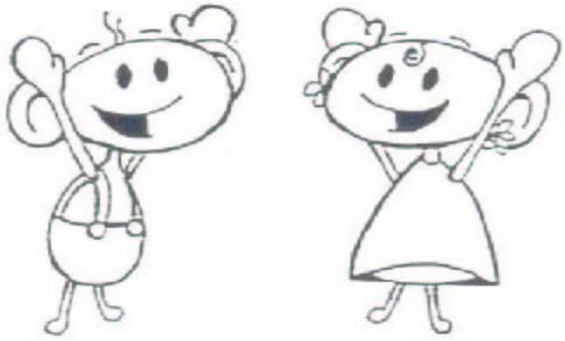
36. Argued with other children or your family?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

In the past 3 months, because of your teeth, lips, mouth or jaws, how often have:

37. Other children teased you or called you names?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

38. Other children made you feel left out?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday

39. Other children asked you questions about your teeth, lips, jaws or mouth?
    - ❑ Never
    - ❑ Once or twice
    - ❑ Sometimes
    - ❑ Often
    - ❑ Everyday or almost everyday



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13. APPENDIX V

Manual of operations BBD7701 Dental

BBD 7701 Version Date: 24Feb2016

Rare Diseases Clinical Research Network

Longitudinal Study of Osteogenesis Imperfecta
BBD #7701
Supplemental: Dental MOO

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Manual of Operations
Version Date: 09February2016

1. DESCRIPTION OF AND INSTRUCTIONS FOR STUDY PROCEDURES

1.1 Dental Assessments

A licensed dental examiner will perform dental assessments for participants with any type of OI at the baseline and 36 month study visits. Assessments will consist of the Oral-Health Quality of Life (OHQOL) questionnaire, panoramic radiographs, oral examination, as well as intraoral and extraoral photographs. Questionnaire and oral examination data will be collected on paper and entered into the online data capture system at the examination sites; images from the panoramic radiographs and intraoral and extraoral photographs will be de-identified, uploaded and evaluated by a central reader (Appendix 1-6).

Before the dental assessments are scheduled to begin the site coordinator or dental examiner will:

- Confirm that consent/assent has been obtained
- Verify that the participant is eligible and has agreed to participate in the dental examination
- Confirm the age of the participant (from the Linking Database)

Before the participant arrives, the dental exam area and equipment will be set up. The following tasks will be performed:

- Wash hands;
- Visually check the following pieces of equipment:
    - The dental light;
    - The air compressor and air tank valves (if applicable); ○ The sterilizer;
    - Turn the air compressor on and close valve (if applicable);
    - Check airflow from air syringe; and
    - Prepare the room for the examination – complete all infection control procedures; ○ Counter tops must be disinfected with an appropriate solution before arranging the instruments and supplies.
    - ○ Disposable barriers must be placed on the following items: chair cover, syringe, light head and controls, and mounted instrument tray.

    - Ensure the following supplies and source documents are available:

    <u>Panoramic radiographs</u>
    - Film, PSP plate, or image sensor and cassette
    - Lead apron and thyroid collar
    - Bite rod
    - Protective sheaths for bite rods and side guides

    <u>Questionnaires</u>
    - Age-appropriate questionnaire
    - Clip board
    - Pen (black or blue)

Oral examination

- 2x2 gauze, non-sterile
- Air water syringe tip
- Sterilized mouth mirror
- Sterilized blunt probe (CPITN)
- Toothbrush
- Floss
- Personal protective equipment
- Dental Clinical Examination Form
- Pen (black or blue)

Intraoral and extraoral photographs

- Canon Rebel T5 camera
- Tamron 90 mm lens
- Canon Macro Ring Lite MR-14EX flash
- Double Sided Plastic Cheek retractors
- Intraoral mirror
- Lip retractor

1.1.1 Examination of Panoramic Radiographs/Panorex

Definition: Panoramic Radiographs help differentiate between a normal and abnormal oral anatomy that are not readily apparent by clinical examination.

Procedure: Panoramic Radiographs

The panoramic radiograph should be performed for participant's ≥ 5 years of age by a trained dental professional who is certified to take radiographs in a clinical setting. The panoramic radiographs will be evaluated by a central reader using the Dental Craniofacial Panorex Evaluation Form (see Appendix 2 and 3).

Performing the Panoramic Radiograph:
Follow institutional and manufacturer's guidelines, including the use of protective sheaths for bite rods and side guides, protective thyroid collars and abdominal shielding. Prior to performing the panoramic radiograph, the dental professional will determine if there are any contraindications to performing the radiograph on the participant.

Step 1. Load film, PSP plate, or image sensor according to manufacturer's guidelines.

Step 2. Set exposure factors based on participant's size and/or age.

Step 3. Ask the participant to remove glasses, jewelry, or other metal objects.

Step 4. Place lead apron on the participant.

Step 5. Position the participant along 3 major axes (anterior-posterior, vertically, and midsagittal) using side guides or positioning lights.

a. Adjust height of machine to accommodate the participant.
b. Ask the participant to:
   - stand or sit up straight to prevent arching of the neck if possible
   - grip the handles
   - rest the chin on the chin rest and bite into the bite rod
   - if standing, position the feet slightly forward
   - relax the shoulders

   Note: Some participants may need special assistance to get a proper and stable position.
c. Position the side guides and/or positioning lights; the participant should look straight ahead with no tilt or tip to the head.

Step 6. Ensure that the shoulders are clear of the machine prior to taking the radiograph, and readjust the participant as needed.

Step 7. Instruct the participant to swallow, place the tongue on the roof of the mouth, breath through the nose, and remain still.

Step 7. Press and hold the exposure button.

Step 9. Acquire the image according to manufacturer's guidelines. Step 10.
Check the image quality and retake if necessary.

1.1.2 Oral-Health Related Quality of Life Questionnaire

Definition: The Oral-Health Quality of Life Questionnaire assesses the impact of oral and craniofacial anomalies on the oral-health related quality of life.

Procedure: The Oral-Health Quality of Life Questionnaire should be given to participant's ≥ 8 years of age (Appendix 7). There are 2 versions of the Oral-Health Quality of Life Questionnaire; one for participants aged 8-10 years of age (CPQ8-10) and one for participants aged 11-14 years of age (CPQ11-14). To assess the quality of life of participants aged 15 years and older, the Oral Health Impact Profile Questionnaire (OHIP-20) will be used. Study personnel will provide the questionnaire to complete on paper and participants will complete the questionnaire using pen in a private room during the yearly study visits.

Study personnel will verify the age of the participant and will provide the corresponding questionnaire and a pen to the participant. Study personnel will explain the purpose of the questionnaire and read the instructions to the participant. The participant will rate various measures of quality of life as it relates to their oral health (perception of oral health, functional well-being, emotional well-being, etc.). Participants will be allowed ample time to complete the questionnaire and study personnel will be available to answer questions during the administration of the questionnaire.

1.1.3 Oral Hygiene and Dental Exam

Definition: The dental exam assesses teeth, dental and intra-oral anatomy, and anomalies.

Procedure: The dental exam, including digital photos, should be performed for participant's ≥ 3 years of age by a trained dental professional. The examination of digital photos will be evaluated by a central reader using the Dental_Craniofacial Photographic Evaluation Form.

Performing the Oral Hygiene and Dental Clinical Exam:

The institution's infection control procedures should be followed. The recorder or dental examiner will help the participant into the dental chair. *Note: Some participants may need special assistance to get a proper and stable position.*

The dental examiner will verbalize his/her observations during the dental exam. The recorder, with the help of the examiner, records the data in the appropriate sections of the Dental Clinical Examination Form (Appendix 8). Data recorded on the Dental Clinical Examination Form will be entered in the online data capture system. A complete description of the online data capture system can be found in section 9 of the MOO.

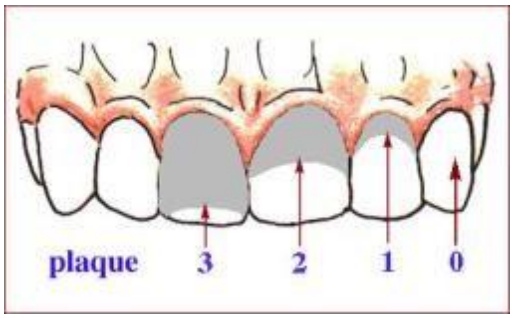
The dentist and recorder will check the hard copy Dental Clinical Examination Form for missing information, errors, and illegible writing before the participant leaves the dental exam room. If information is missing, the dentist may need to reexamine an area of the mouth.

1.1.4.1 Oral Hygiene:

Oral Hygiene will be assessed on participants' ≥ 4 years of age according to the criteria established in the Debris Index of the Simplified Oral Hygiene Index [1,2].

Scores	Criteria
0	**No debris or stain present**
1	**Soft debris covering not more than one third of the tooth surface, or presence of extrinsic stains without other debris regardless of surface area covered**
2	**Soft debris covering more than one third, but not more than two thirds, of the exposed tooth surface**
3	**Soft debris covering more than two thirds of the exposed tooth surface**

Criteria for classifying debris



Tooth and surface selection

Participants aged 4-6 years:

- Posterior teeth - The buccal surface of the upper right (UR) first primary molar (4) and lingual surface of the lower left (LL) second primary molar (5) will be examined.
- Anterior teeth - The buccal surfaces of the upper left (UL) primary central incisor (1) and lower right (LR) primary lateral incisor (2) will be examined.
  If any of the teeth are missing, the corresponding tooth on the opposite side of the midline will be used. For example, if the upper right (UR) first primary molar (4) is missing, the upper left (UL) first primary molar (4) will be examined**.**

Participants aged 7-10 years:

- Posterior teeth - The buccal surfaces of the upper right (UR) first primary molar (4) and upper left (UL) permanent first molar (6) and lingual surfaces of the lower left (LL) second primary molar (5) and first permanent lower right (LR) molar 6 will be examined.
- Anterior teeth - The buccal surfaces of the upper left (UL) primary central incisor (1) and lower right (LR) primary lateral incisor (2) will be examined.
  If any of the teeth are missing or are unable to be assessed (teeth with orthodontic brackets, etc.), the corresponding tooth on the opposite side of the midline will be used. For example, if the upper right (UR) first primary molar (4) is missing, the upper left (UL) first primary molar (4) will be examined.

Permanent dentition: Surfaces are selected from 4 posterior and 2 anterior teeth.

- Posterior teeth - The buccal surface of the permanent upper first molars and the lingual surface of the permanent first molars will be examined.
- Anterior teeth - The buccal surfaces of the permanent upper right (UR) and lower left (LL) central incisors will be examined. If the permanent upper right (UR) or lower left (LL) central incisor is missing, the central incisor on the opposite side of the midline will be used.

A mean debris index (average score per number of surfaces scored) will be calculated per child. The mean debris index should range from 0-3. At least two of the six possible surfaces must have been examined for an individual score to be calculated.

Debris Index = (The buccal-scores) + (The lingual-scores) / (Total number of examined buccal and lingual surfaces).

Mean debris scores will be categorized as follows and the classification will be recorded on the Dental Clinical Examination Form:

Scores	Classification
<0.9	Good
1 – 1.9	Fair
>2	Poor

1.1.3.2 Dental Exam

The following assessments will be conducted for both the primary and permanent tooth charts using the dental examination data and dental radiographs: Note: The dental examination of the permanent dentition does not include 3rd molars.

Presence:

a. If the tooth is present,
   - Circle the tooth number at the top of the chart.
   - In the next row labeled “Present or Missing”, place the number “0” in the box directly below the tooth number.

b. If the tooth is missing
   - Make an “X” through the tooth number at the top of the chart.

Ask the participant if the missing tooth was extracted because it was decayed or had periodontal disease. If it was extracted, in the next row labeled “Present or Missing”, place the number “1” in the box directly below the tooth number. If the tooth was never present or was removed for orthodontic reasons, place an “X” in the box directly below the tooth.

Caries Assessment:

Visual examination will be used to assess participants' caries status. Prior to performing the dental exam study personnel will receive training and be calibrated for the caries classification.

The training and calibration is based on the International Caries Detection and Assessment System (ICDAS)[3] measurements and coding back to the WHO code. ICDAS uses measurements 0-6 to classify the stages of caries, while WHO uses measurements 0-9 for condition/status where sound teeth are coded as 0 and teeth with caries are coded as 1.[4] The online ICDAS eLearning may be accessed using the following hyperlink: https://www.icdas.org/elearning-programmes.

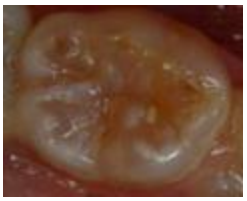
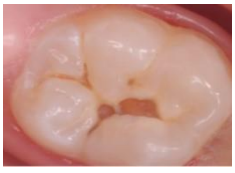
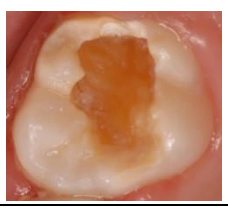
Prior to the caries examination and following the oral hygiene assessment, participant's teeth will be cleaned via a round of tooth flossing and brushing by study personnel. The armamentarium for the examination will include a toothbrush, dental floss, plane mouth mirror, a 3-in-1 air water syringe and a blunt probe (CPITN). Teeth will be examined both wet and after drying with compressed air to improve the clinical assessment of all tooth surfaces. Note: The caries examination does not include 3rd molars.

Table 1: Classification of carious status based on the ICDAS Criteria

Collapsed Codes	Code	Criteria
0	0	Sound tooth surface, with no visual changes indicative of caries.
	1	First visual change in enamel (seen only after prolonged air drying or restricted to the confines of a pit or fissure
	2	Distinct visual change in enamel. When wet, there is a carious opacity (white spot lesion) and / or brown carious discoloration which is wider than the natural fissure / pit
1	3	Initial localized enamel breakdown, without clinically visual signs of dentinal involvement
	4	Underlying dark shadow from dentin, with or without enamel breakdown. The shadow may appear as grey, blue, or brown in color
	5	Distinct cavity with visible dentin cavitation in opaque or discolored enamel with exposed dentin in the examiner's judgment
	6	Extensive distinct cavity with clearly visible dentin. The cavity is both deep and wide. Dentin is clearly visible on both the walls and at the base.

(Supporting information can be found at www.icdas.org)

Table 2: ICDAS codes for clinical visual assessment based on the extent of caries lesions.

Collapsed Codes	Code	Description	A (normal population)	B (OI patients)
0	0	Sound tooth surface		
	1	First visual change in enamel		
	2	Distinct visual change in enamel		
1	3	Initial localized enamel breakdown		
	4	Underlying dark shadow from dentin		
	5	Distinct cavity visible dentin cavitation		
	6	Extensive distinct cavity		

Note: Column A shows ICDAS scores in permanent molars of normal population. Column B shows ICDAS scores in permanent molars of Osteogenesis imperfecta (OI) patients with or without Dentinogenesis imperfecta (DI).

For this study, teeth with ICDAS measurements 0-2 will be considered sound and recorded as 0; teeth with ICDAS measurements 3-6 will be considered carious and recorded as 1.

a. If the tooth does not have caries (ICDAS 0, 1, or 2), place the number “0” in the box below the tooth number in the row marked “Caries.”
b. If the tooth has caries (ICDAS 3, 4, 5, or 6), place the number “1” in the box below the tooth number in the row marked “Caries.” **Fillings** (any type of filling, including a crown):
    a. If the tooth does not have any type of filling, place the number “0” in the box below the tooth number in the row marked “Filled.”
    b. If the tooth has any type of filling, place the number “1” in the box below the tooth number in the row marked “Filled.” It does not matter how large the filling on the tooth is; any tooth with a filling is given a "1".
    c. If the tooth has a sealant but no filling, place the number “0” in the box below the tooth number in the row marked “Filled.”
    d. If the tooth has any type of filling in addition to the sealant, place the number “1” in the box below the tooth number in the row marked “Filled.” *Ectopic eruption*:

An ectopic eruption is present if the crown of the tooth is either on the labial or the lingual side of the dental arch.

a. If the total crown of the tooth is located within the line of best fit of the dental arch, place the number 0 in the row marked “ectopic eruption”.
b. If the total crown of the tooth is located outside the line of best fit of the dental arch, place the number 1 in the row marked ectopic eruption.

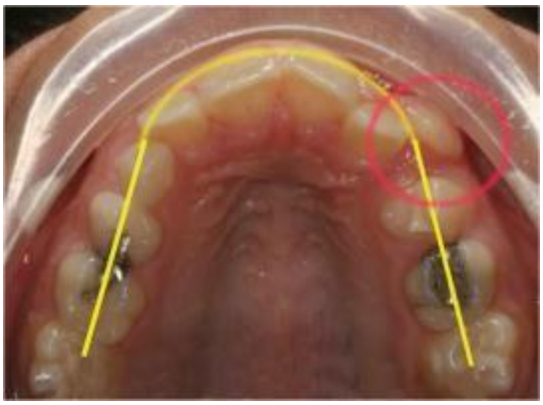


Figure 1. Assessment of ectopic eruption. The yellow line represents the line of best fit of the dental arch. The crown of the tooth in the red circle is located on the labial side of the yellow line. A score of 1 is attributed to the upper left canine.

***Dentinogenesis Imperfecta*:**

In dentinogenesis imperfecta, the teeth can be discolored and appear opalescent / blue grey or yellow / brown. Indicate if the dentition is discolored in a manner that is consistent with dentinogenesis imperfecta (DI) in the row labeled "Color of Dentition."

a. If the dentition does not demonstrate any discoloration, check the box "Normal with no evidence of dentinogenesis imperfecta."
b. If the dentition has teeth with the characteristic opalescent / blue gray discoloration of DI, check the box "q Opalescent / Blue gray discoloration."

c. If the dentition has teeth with the characteristic yellow / brown discoloration of DI, check the box "q Yellow / Brown discoloration."

Figure 2. Dentinogenesis imperfecta. In the left panel teeth appear more severely affected by DI than in the right panel. However, both cases would be evaluated as 'DI present'.

***Occlusion*:**

The occlusion and position and malrelations of the teeth will be examined and recorded as part of the dental exam. During the occlusal assessments the participants' jaws should be closed in centric relation and the following oral assessments will be conducted:

The centric relation position is defined as the position where a pure hinge movement without mandibular deviation can be repeatedly performed. Manipulate the patient's mandible in centric relation to ensure that the condyles are properly seated in the glenoid fossa to insure a reproducible bite.

The molar and canine relation will be assessed on the right and left sides.

Canine Classification

- Class I: The upper canine is positioned in the embrasure between the lower canine and first lower premolar.
- Class II: The upper canine is positioned mesially to the embrasure between the lower canine and first premolar.
- Class III: The upper canine is positioned distally to the embrasure between the lower canine and first premolar.

Molar Classification

- Class I: The mesio buccal cusp of the upper first permanent molar is in contact or in line with the mesio buccal groove of the lower first permanent molar.
- Class II: The mesio buccal cusp of the upper first permanent molar is positioned anteriorly to the mesio buccal groove of the lower first permanent molar.
- Class III: The mesio buccal cusp of the upper first permanent molar is positioned posteriorly to the mesio buccal groove of the lower first permanent molar.

Class I molar and canine occlusion

Figure 3. At the molar level, the red line goes through the upper molar mesial cusp and the lower molar buccal groove indicating Class I Angle relationship. At the canine level, the redline goes through the incisal tip of the upper canine and passes through the embrasure between the lower canine and first premolar indicating a Class I canine relationship.

Class II molar and canine occlusion

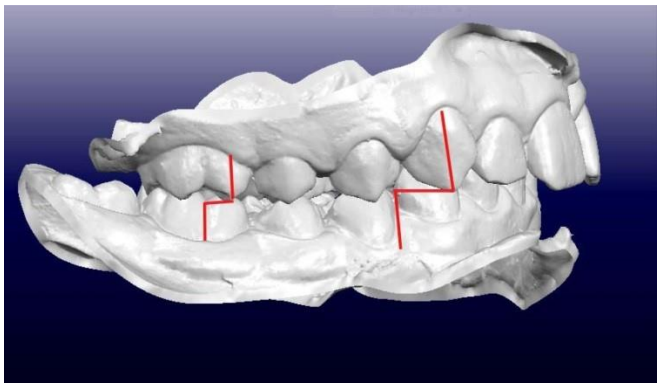


Figure 4. The red line going through the mesiobuccal cusp of upper first molar is located mesially (anteriorly) to the buccal groove of the lower first molar, resulting in a Class II molar relationship. The line going through the incisal tip of the upper canine is located mesially to the line passing through the embrasure between the lower canine and first premolar, resulting in a Class II canine relationship.

Class III molar and canine occlusion

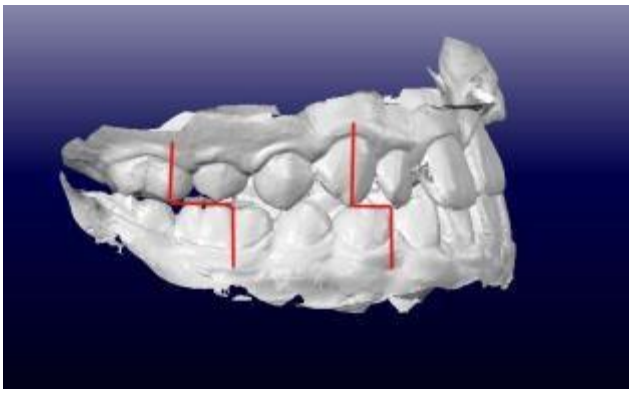


Figure 5. The red line going through the mesiobuccal cusp of upper first molar is located distally (posteriorly) to the buccal groove of the lower first molar, resulting in a Class III molar relationship. The line going through the incisal tip of the upper canine is located distally to the line passing through the embrasure between the lower canine and first premolar, resulting in a Class III canine relationship.

Overbite:

The amount overlap of the lower incisor by the upper incisor in centric relation will be assessed. The overbite is calculated as a percentage of the lower central incisor crown that is covered by the upper incisor. If the upper incisors edges are on the same level as the lower incisor edges, the overbite is 0%. If the upper incisor covers half the lower incisor crown, the overbite is 50%. If the upper incisor covers the lower incisor crown entirely, the overbite is 100%.

Figure 6. If the upper incisors edges are on the same level as the lower incisor edges, the overbite is 0%.

Figure 7. 10% overbite. Present when the upper incisors cover 10% of the lower incisor crown.

Figure 8. 25% overbite. Present when the upper incisors cover 25% of the lower incisor crown.

Figure 9. 50% overbite. Present when the upper incisors cover 50% of the lower incisor crown.

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Figure 10. 75% overbite. Present when the upper incisors cover 75% of the lower incisor crown.

Figure 11. 100% overbite. Present when the upper incisors cover 100% of the lower incisor crown.

Openbite:

The incisal contact between fully erupted maxillary and mandibular teeth will be assessed. Teeth will be considered fully erupted when the junctional epithelium is at the cemento-enamel junction. If the upper incisors do not make contact with the lower incisors in the vertical plane, an anterior openbite is present.

a. If an openbite is not present, select “No” for Openbite
b. If an openbite is present, select “Yes” for Openbite

Figure 12. Anterior openbite

Lateral Openbite:

The occlusal contact between fully erupted maxillary and mandibular teeth will be assessed. Teeth will be considered fully erupted when the junctional epithelium is at the cemento-enamel junction. If one or several posterior teeth are not in occlusal contact in maximum interdigitation, a lateral openbite is present. The way to measure the openbite is to assess the longest distance between the buccal cusps of the maxillary and mandibular posterior teeth with a plastic ruler or a caliper. The largest linear measurement from the cusps of the maxillary premolars or molars and with the mandibular premolars or molars, regardless of side, will be recorded.

a. If no lateral openbite is present, select “No”
b. If the largest lateral openbite measurement is 0mm to 1mm, select “1mm”
c. If the largest lateral openbite measurement is 1+mm to 3mm, select “3mm”
d. If the largest lateral openbite measurement is 3+mm, select “over 3mm”

Figure 13. Lateral Openbite. The posterior teeth have failed to completely erupt and are not in maximum interdigitation. There is lack of contact of the upper and lower dentition, resulting in a lateral posterior openbite.

Overjet:

The overjet or horizontal distance between the incisal edges of the maxillary incisors and mandibular incisors will be recorded as positive, negative, or edge to edge.

- Positive overjet: distance between the incisal edge of the maxillary incisors and the labial surface of the lower central incisor in centric relation.

Figure 14. Positive overjet

Negative overjet: A negative overjet is recorded when the lower incisors are positioned anteriorly to the upper incisors in maximum interdigitation.

Figure 15. Negative overjet

Edge to edge: If the upper and central incisors are in contact in maximum interdigitation, then the overjet is absent and measured as 0 mm.

Figure 16. Edge to edge occlusion

Dental Midline:

The upper and lower dental midlines will be measured and recorded. The upper dental midline will be assessed in relation to the reference midline. The reference midline is obtained by connecting Glabella (a point located in the center of the eyebrows) and subnasale (a central point located 5 mm under the base of the nose).

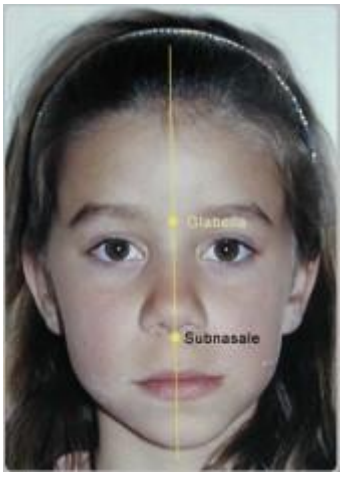


Figure 17. Reference midline (yellow line)

The upper dental midline alignment should be first assessed in relation to the reference midline. The amount of deviation of the upper dental midline is obtained by measuring the difference between the reference midline and the upper dental midline using a plastic ruler.

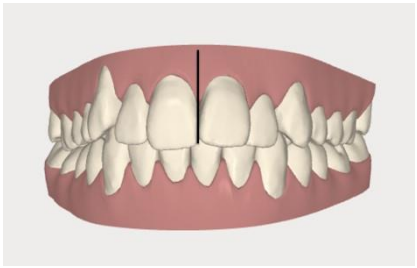


Figure 18. The upper dental midline is located between the upper central incisors.

a. If the upper midline deviation measurement is 0mm to 1mm, select “1mm”
b. If the upper midline deviation measurement is 1+mm to 3mm, select “3mm”
c. If the upper midline deviation measurement is 3+mm, select “over 3mm”

The lower midline position will be assessed in relation to the reference midline. The amount of deviation of the lower dental midline is obtained by measuring the difference between the reference midline and the lower dental midline.

Figure 19. The lower dental midline is located between the lower central incisors.

a. If the lower dental midline measurement is 0mm to 1mm, select “1mm”
b. If the lower dental midline measurement is 1+mm to 3mm, select “3mm”
c. If the lower dental midline measurement is 3+mm, select “over 3mm”

Posterior Crossbite:

The posterior teeth will be assessed to determine if the buccal cusps occlude in a lingual position. If one or more buccal cusps of posterior teeth occlude in a lingual position in relation to the buccal cusps of the mandibular teeth, a posterior crossbite is present.

a. If a posterior crossbite is present, select “yes” for Posterior Crossbite.
b. If a posterior crossbite is not present, select “no” for Posterior Crossbite.

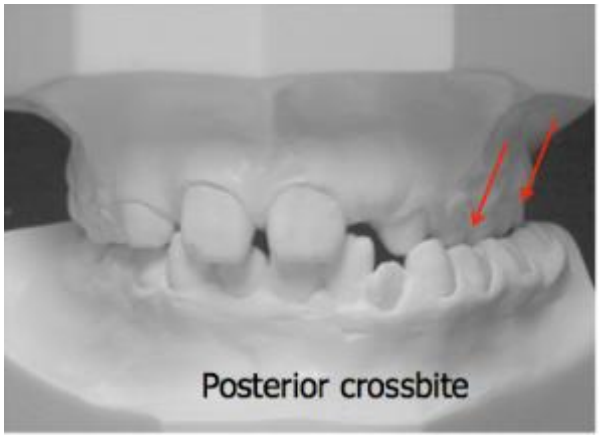


Figure 20. The upper posterior teeth are in a lingual position and the buccal cusps actually occlude in the central fossa of the lower teeth resulting in a posterior crossbite (red arrows) *Anterior Crossbite*:

The anterior teeth will be assessed to determine if the maxillary anterior teeth are in a lingual position. If one or more of the maxillary teeth are in a lingual position in relation to the mandibular teeth, an anterior crossbite is present.

a. If an anterior crossbite is present, select “yes” for Anterior Crossbite.
b. If an anterior crossbite is not present, select “no” for Anterior Crossbite.

Figure 21. Anterior Crossbite

References

1. Greene JG, Vermillion JR. The Simplified Oral Hygiene Index. J Am Dent Assoc. 1964; 68(1): 7-13.
2. Rodrigues CR, Ando T, Guimarães LO. Simplified oral hygiene index for ages 4 to 6 and 7 to 10 (deciduous and mixed dentition). Rev Odontol Univ Sao Paulo. 1990; 4(1): 2024.
3. Iranzo-Cortés JE, Montiel-Company JM, Almerich-Silla JM. Caries diagnosis: agreement between WHO and ICDAS II criteria in epidemiological surveys. Community Dent Health. 2013; 30(2): 108-111.
4. World Health Organization. Oral Health Surveys: Basic Methods. 4th ed. Geneva: World Health Organization; 1997 (42-44)

1.1.4 Digital Photos:

Definition: Intraoral and Extraoral photographs will be used to assess and confirm dental and oral anatomy and anomalies.

Procedure: Intraoral and Extraoral Photographs
Intraoral and extraoral photographs should be performed for participant's ≥ 3 years of age by a trained dental professional. The intraoral and extraoral photographs will be evaluated by a

central reader using the Dental Craniofacial Photographic Evaluation Form (Appendix 5 and 6).

Instructional videos for intraoral and extraoral photography may be accessed by logging into the RDCRN member's website and navigating to the media center. Videos are titled BBD 7701 Dental 1, 2 and 3.

Equipment:
The following equipment will be used for both intraoral and extraoral photographs:

Camera Box
• Canon Rebel T5

Lens
• Tamron 90 mm

Flash

- Canon Macro Ring Lite MR-14EX

For assistance with the camera or accessories, please contract Dr. Retrouvey (Jeanmarc.Retrouvey@mcgill.ca) or the Lester Dine company (www.dinecorp.com) and identify yourself as being part of the BBDC consortium.

Extraoral Photos:

All extraoral photographs should be taken using white or neutral background, standardized lighting (note: a light box may be used to alleviate shadows), and taken in portrait format.

Camera settings:

The following settings should be used for extraoral photographs:

Set camera on Manual; never use the Auto set up.

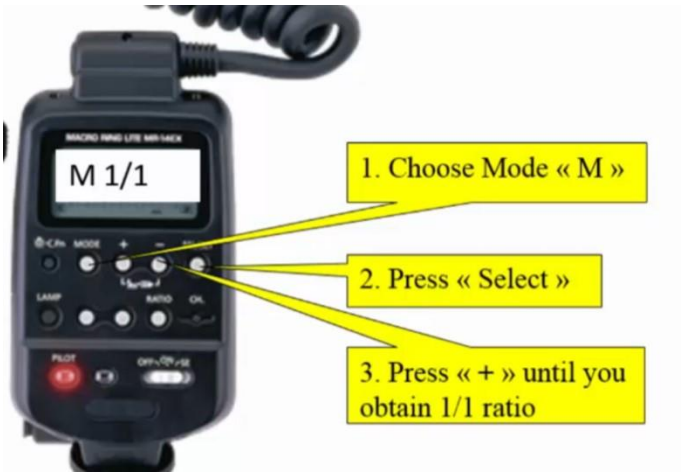
- Aperture 11 (9 to 10 for darker skin subjects)
- Automatic Focus (AF) .48m to ∞
- Flash Mode “M” 1/1 Camera Box:
- ISO 200 ○ Speed: Shutter speed 1/125 ○ Aperture:
- F stop: 9 (dark skin) 11 (fair complexion)

Lens:

- Focus switch on .48m to ∞ ○ Focus switch: automatic focus (AF)

Flash Ring :

- Flash Mode “M” 1/1



Performing Extraoral Photography:

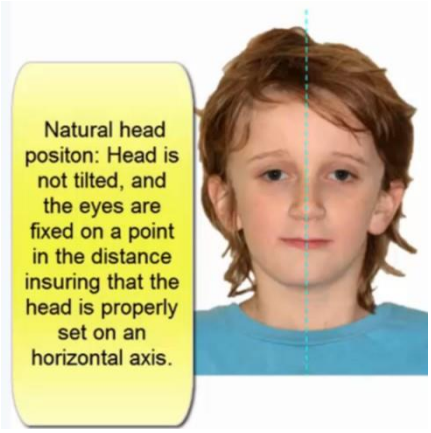
Step 1. Confirm camera and equipment settings.

Step 2. Ask the participant to:

- Remove coats and hoodies, and/or turn down collar.
- Remove or arrange head scarves so the patient's ears and jaw line are clearly visible.
- Take out any removable appliances (unless otherwise requested).
- Remove glasses, visible jewelry and/or body piercings.
- Position the hair so that it does not obscure the face or ears.

Step 3. Position the participant for Face and Smile photographs:

- Participant may be standing or sitting in a wheelchair or dental chair (depending on OI condition).
- If a light box is not being used, position the participant away from the wall to avoid shadows.
- The participant should look straight at the camera.
- Participant's eyes should be open.
- Face and lips should be in relaxed natural position (lips together or slightly apart).
- Participant should be biting gently on their back teeth (avoid clenching).
- Participant's head should be straight (not tilted) and leveled (horizontal Frankfort plane).



Step 4. Position the camera in regards of the participant:

- Position the camera vertically.
  - Adjust to the participant's position.
  - Maintain the camera as parallel to the natural head position as possible.
- Camera positioned with lens axis horizontal at patient's level (not looking up or down at patient). Note: the photographer may have to adjust their position depending on the participant's height and/or angulation.
- Use camera viewfinder's grid to verify patient's position.

Step 5. Take Face photograph and check the image quality on the camera screen; retake if necessary.

Step 6. Take Smile photograph:

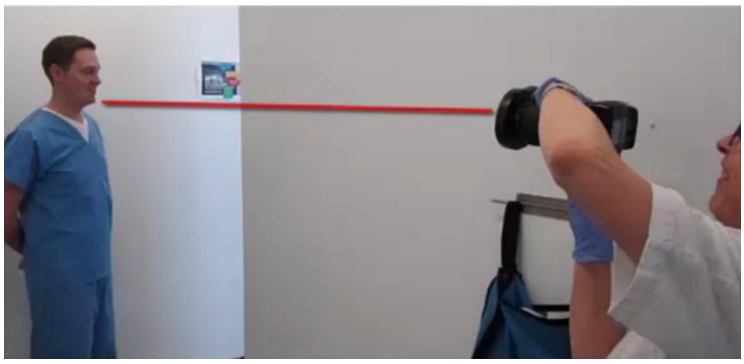
- Ask the participant to smile with a natural, unstrained smile. The lips should be slightly apart so the dentition can be seen in relation to the smile line.
- Check the image quality and retake if necessary.

Step 7. Position the participant for 45º Profile and 45º Smiling photographs:

- Participant may be standing or sitting in a wheelchair or dental chair (depending on OI condition).
- If a light box is not being used, position the participant away from the wall to avoid shadows.
- The participant should be positioned 45° from the camera and looking straight ahead (not at the camera).
  - The inside corner of the distal eye should be in line with the nose.
- Participant's eyes should be open.
- Face and lips should be in relaxed natural position (lips together or slightly apart).
- Participant should be biting gently on their back teeth (avoid clenching).
- Participant's head should be straight (not tilted) and leveled (horizontal Frankfort plane).

8. Position the camera in regards of the participant:

- Position the camera vertically.
  - Adjust to the participant's position.
  - Maintain the camera as parallel to the natural head position as possible.
- Camera positioned with lens axis horizontal at patient's level (not looking up or down at patient). Note: the photographer may have to adjust their height depending on the participant's height and/or position.
- Use camera viewfinder's grid to verify patient's position.



Step 9. Take 45º (Oblique) Profile photograph and check the image quality; retake if necessary.

Step 10. Take Smiling 45º (Oblique) Profile photograph:

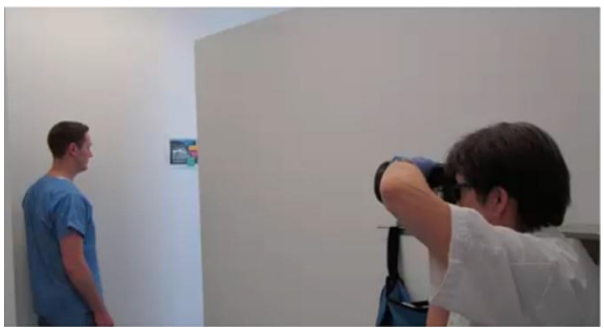
- Ask the participant to smiles with a natural, unstrained smile. The lips should be slightly apart so the dentition can be seen in relation to the smile line.
- Check the image quality and retake if necessary.

STEP 11. Position the participant for Profile and Smiling Profile photographs:

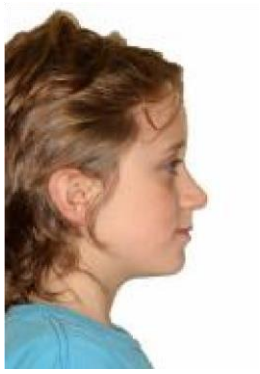
- Participant may be standing or sitting in a wheelchair or dental chair (depending on OI condition).
- If a light box is not being used, position the participant away from the wall to avoid shadows.
- The participant must be positioned 90° from the camera and looking straight ahead (not at the camera). ○ The participant should be positioned to their left (to obtain a photograph of the right profile).
- Participant's eyes should be open.
- Face and lips should be in relaxed natural position (lips together or slightly apart).
- Participant should be biting gently on their back teeth (avoid clenching).
- Participant's head should be straight (not tilted) and leveled (horizontal Frankfort plane).

Step 12. Position the camera in regards of the participant:

- Position the camera vertically.
  - Adjust to the participant's position.
  - Maintain the camera as parallel to the natural head position as possible.
- Camera positioned with lens axis horizontal at patient's level (not looking up or down at patient). Note: the photographer may have to adjust their height depending on the participant's height and/or position.
- Use camera viewfinder's grid to verify patient's position.



Step 13. Take Full Profile photograph and check the image quality; retake if necessary.



STEP 14. Take Smiling Full Profile photograph:

- Ask the participant to smiles with a natural, unstrained smile.
- Check the image quality and retake if necessary.

Correct Extraoral Photographs:

All extraoral photographs should have the same proportions, the eye line should be parallel to the floor, and the head should be positioned in the natural position and not tilted within the 3 planes of space.

Common Extraoral Photographs Errors include:

Intraoral Photos:

After taking extraoral photographs reposition the participant in the dental chair and set dental chair to proper height to take pictures at the correct angulation.

All intraoral photographs should be taken in portrait format. Note: intraoral photographs should be taken after the oral examinations (i.e., following tooth brushing) for better visibility.

Frontal and Lateral Intraoral Photographs

Equipment:

The following equipment will be used for frontal and lateral intraoral photographs:

Double Sided Plastic Cheek retractors (large and small tips) Note:
use proper size side depending on age and tissue elasticity.

The following settings should be used for the frontal and lateral intraoral photographs:

Camera settings:

Set camera on Manual; never use the Auto set up.

- Aperture 20 to 22 ○ Automatic Focus (AF) .3m to ∞ ○ Flash Mode “M” 1/4 Camera Box: ○ Iso 200 ○ Speed: Shutter speed 1/125 ○ F stop: 16 to 22
- Manual focus

Lens:

- Focus switch on .31m to ∞
- Focus switch: automatic focus (AF)

Flash Ring:

- Flash Mode “M” 1/4

Performing Frontal Intraoral Photography:

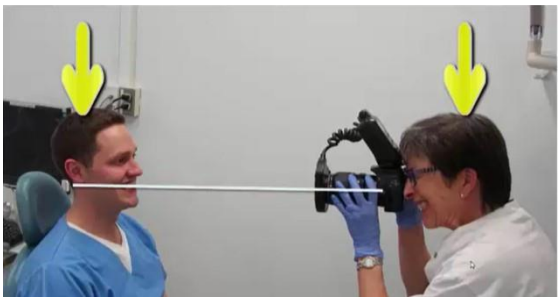
Step 1. Confirm camera and equipment settings.

Step 2. Ask the technician or participant to retract the cheeks away from the teeth.

- Ask the participant or technician pull the cheek retractors away from teeth but also forward (not backwards towards the ears). The cheek retractors should be 90 degrees to the camera. ○ Lips should be retracted so that the teeth and gums show including posterior buccal areas.
- Ask the participant to bite gently on their back teeth (avoid clenching).

Step 3. Position the camera

- Position the camera horizontally.
    - Head of the photographer and participant should be at the same height.
- Camera must be parallel to the occlusal plane so that the occlusal plane is horizontal in the photo.
- Camera is positioned at a 90 degree angle towards the line best fit of the participant's face.
- Facial midline should be centered in the photo.
- Central and lateral incisors should be in full focus.



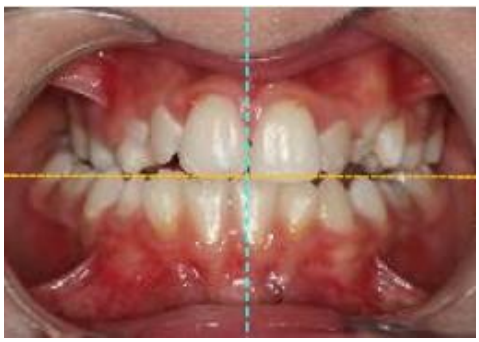
Step 4. Take frontal intraoral photograph and check the image quality; retake if necessary.

Correct Frontal Intraoral Photographs

All frontal intraoral photographs should meet the following criteria:

- Facial midline centered in the photo
- Occlusal plane is horizontal in the photo (unless not applicable: canted plane, asymmetry)
- Teeth not deformed by a parallaxing effect

Examples:



Common Frontal Intraoral Photographs Errors include:

- Incorrect angulation of the camera
- Not using cheek retractors
- Overexposure

Examples:

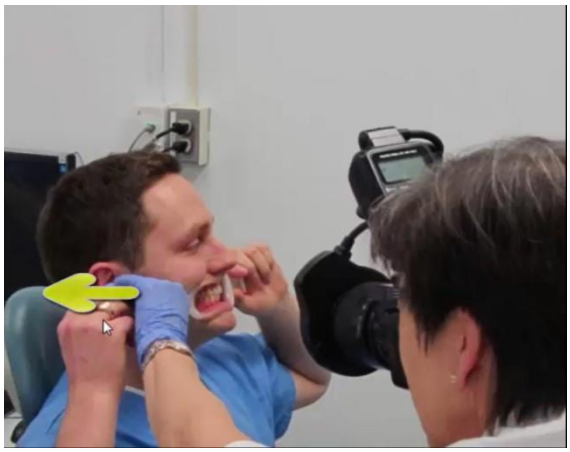
Performing Lateral Intraoral Photography:

Lateral photographs are used to help determine molar occlusion. Step 1. Confirm camera and equipment settings.

Right Side

Step 2. Ask the technician or participant to retract the right cheek away from the teeth using the small side of the retractor. Note the left side will be using the large side of the retractor unless age and tissue elasticity necessitate the use of the small side.

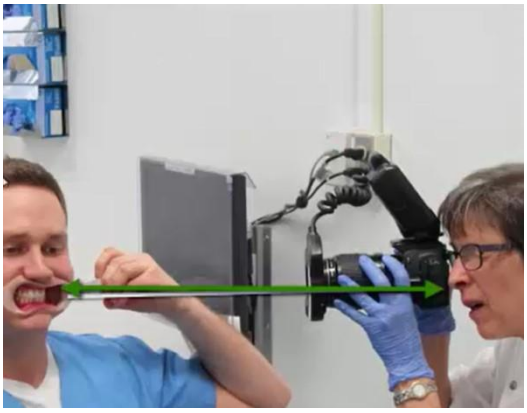
- Ask the participant or technician pull the right cheek retractor towards the ear and relax the left cheek retractor.
- Confirm that the molars are exposed.



Step 3. Ask the participant to practice habitual occlusion so they will not move. Participants with OI type 3 and 4 may have lateral open bites causing the bite to be unstable.

Step 4. Position the camera

- Position the camera horizontally.
- Camera must be parallel to the occlusal plane so that the occlusal plane is horizontal in the photo.
- Camera is positioned at a 90 degree angle towards the line of dentition.
- Canine area should be centered as much as possible in the photo.
- First molar should be visible. If the second molar is present, it should be partly visible.
- Incisors should not be abutting the edge of the photo.



Step 5. Take right lateral photograph and check the image quality.

Left Side

Step 6. Ask the technician or participant to retract the left cheek away from the teeth using the small side of the retractor. Note the right side will be using the large side of the retractor unless age and tissue elasticity necessitate the use of the small side.

- Ask the participant or technician pull the left cheek retractor towards the ear and relax the right cheek retractor.
- Confirm that the molars are exposed.

Step 7. Ask the participant to practice habitual occlusion so they will not move. Participants with OI type 3 and 4 may have lateral open bites causing the bite to be unstable.

Step 8. Position the camera

- Position the camera horizontally.
- Camera must be parallel to the occlusal plane so that the occlusal plane is horizontal in the photo.
- Camera is positioned at a 90 degree angle towards the line of dentition.
- Canine area should be centered in the photo.
- First molar should be visible. If the second molar is present, it should be partly visible.
- Incisors should not be abutting the edge of the photo.

Step 9. Take left lateral photograph and check the image quality; retake if necessary.

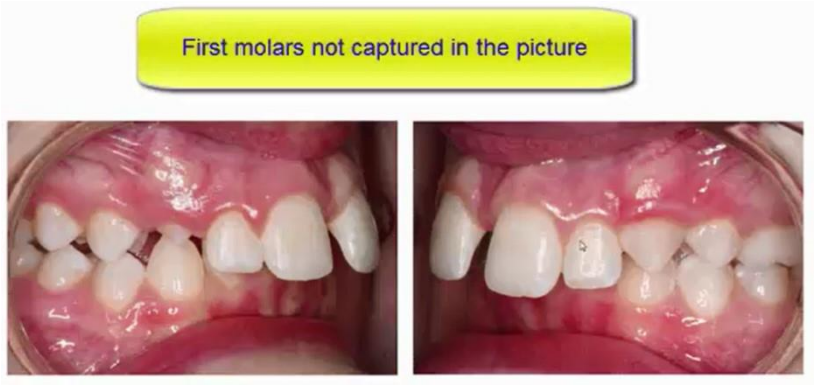
Correctly taken Lateral Intraoral Photographs

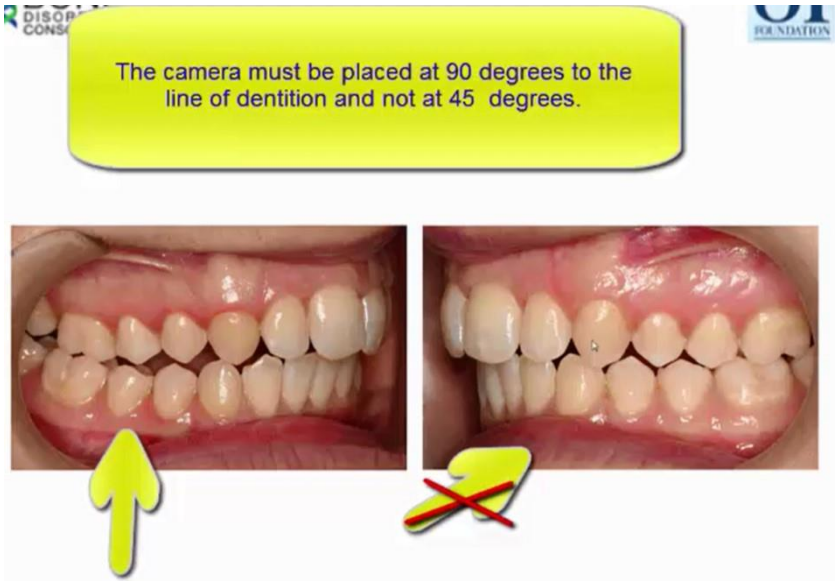
All lateral intraoral photographs should meet the following criteria: •
Camera placed at 90 degrees to the line of dentition

- Molars present
- Cheek retractors pushed away
- Occlusal plane is present

Examples:

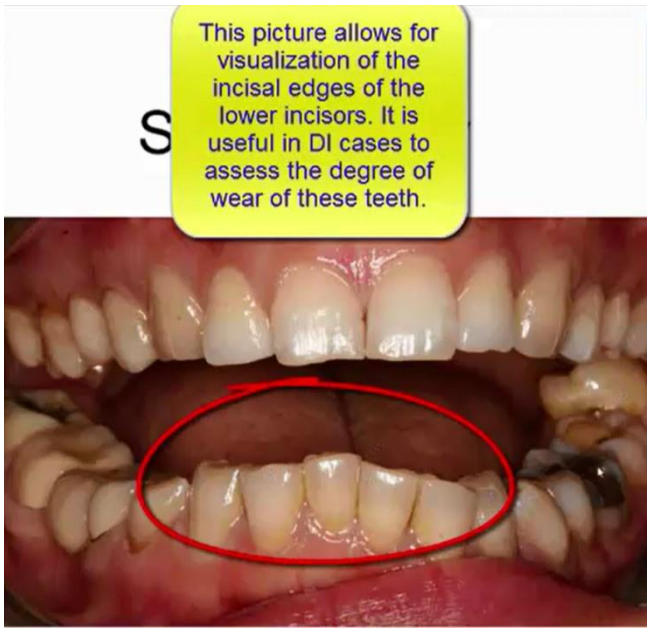
Common Lateral Intraoral Photographs Errors include:





Performing Special View Intraoral Photography: (optional)

In some cases, especially those with dentinogenesis imperfect, it is helpful to obtain special view intraoral photos in order to assess the degree of wear on the mandibular incisors. Special view intraoral photos are similar to frontal view, with the exception that special view photos capture the incisal edges of mandibular incisors.



Step 1. Confirm camera and equipment settings.

Step 2. Ask the technician or participant to retract the cheeks away from the teeth.

- Ask the participant or technician pull the cheek retractors away from teeth but also forward (not backwards towards the ears). The cheek retractors should be 90 degrees to the camera.
  - Lips should be retracted so that the teeth and gingival tissues show including posterior buccal areas.
- Ask the participant to open their mouth slightly (the incisal edges of the mandibular incisors should be visible).

Step 3. Position the camera

- Position the camera horizontally.
  - Head of the photographer and participant should be at the same height.
- Camera must be parallel to the occlusal plane so that the occlusal plane is horizontal in the photo.
- Camera is positioned at a 90 degree angle towards the line best fit of the participant's face.
- Facial midline should be centered in the photo.
- Central and lateral incisors should be in full focus.

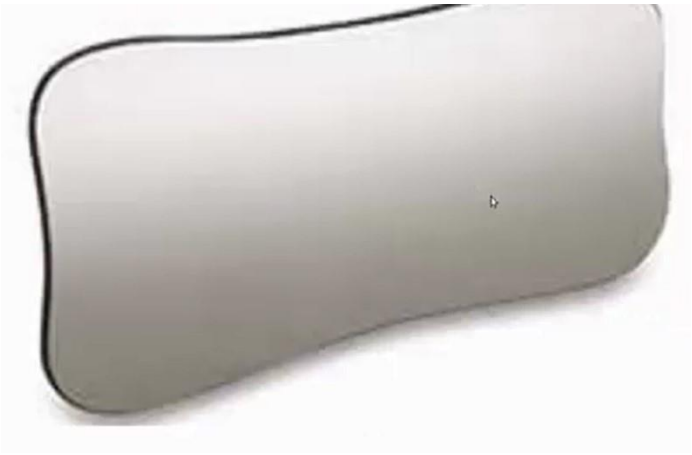
Step 4. Take the special view intraoral photograph and check the image quality; retake if necessary.

Occlusal Intraoral Photographs

Equipment:

The following equipment will be used for occlusal intraoral photographs:

Intraoral mirror



Lip retractor-to avoid interference and get lips out of shot

The following settings should be used for the occlusal intraoral photographs:

Camera settings:

Set camera on Manual; never use the Auto set up.

- Aperture 16 ○ Manual Focus (MF) .3m to ∞ ○ Flash Mode “M” 1/4 Camera Box:
- Iso 200
- Speed: Shutter speed 1/125 ○ F stop: 16 to 22 ○ Manual focus

Lens:

- Focus switch on .31m to ∞
- Focus switch: automatic focus (AF)

Flash Ring:

- Flash Mode “M” 1/4

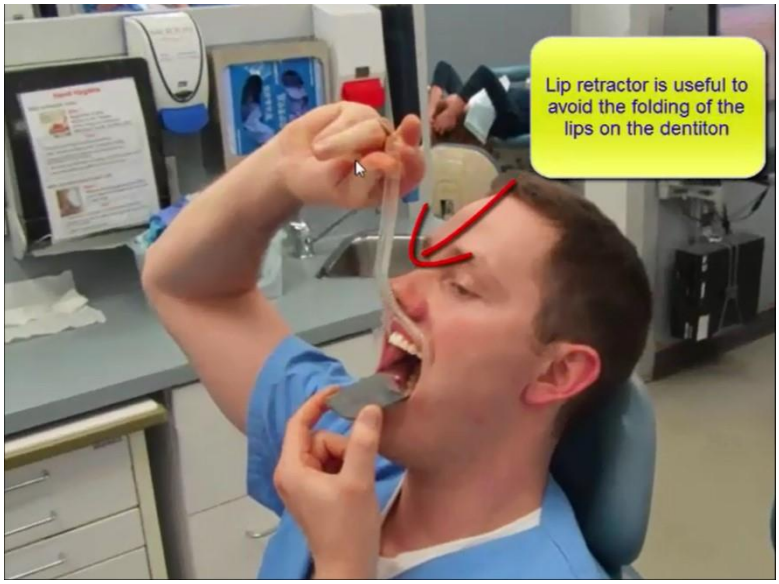
Performing Occlusal Intraoral Photography:
Occlusal photographs should use the same angle and magnification.

Step 1. Confirm camera and equipment settings.

Maxillary Occlusal

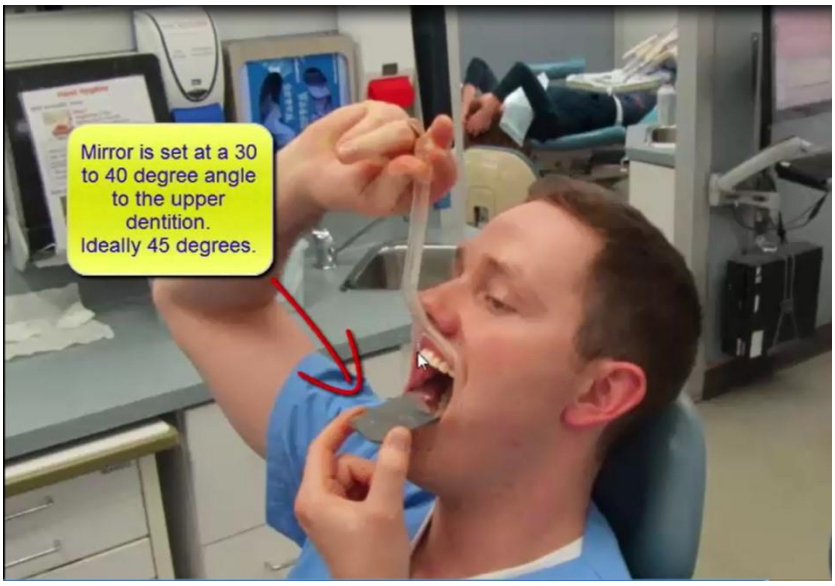
Step 2. Ask the technician or participant to retract the maxillary lip away from the teeth.

- Ask the technician or participant to hold the lip retractor to retract the maxillary lip so that the maxillary teeth are visible.



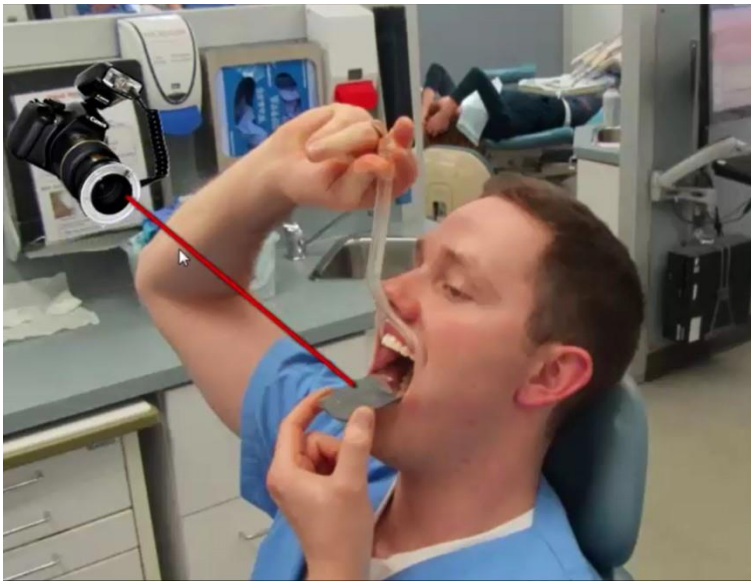
Step 3. Position the occlusal mirror.

- Insert the at a 30 to 40 degree angle to the maxillary teeth.
  - The mirror should be placed gently to the distal of the last molar.
  - Ask the technician or participant to hold the mirror in position.



Step 4. Position the camera

- Position the camera horizontally.
- Aim camera into the mirror at a 45 degree angle



Step 5. Take maxillary occlusal photograph and check the image quality; retake if necessary.

Correct Maxillary Occlusal Intraoral Photographs

All maxillary intraoral photographs should meet the following criteria:

- The entire arch should be visible in the photo.
- The image is parallel to the occlusal plane.
- The arch is centered in the photo.
- The edge of the mirror does not interfere with the photo.

- All incisors are normal shape and appear properly aligned
- No fog or water spots visible in the photo.
- No shadow at the posterior area of the photo.

Example:

Common Maxillary Occlusal Intraoral Photographs Errors include:

- Aiming camera straight at teeth without mirror
- All teeth are not present
- Poor angulation

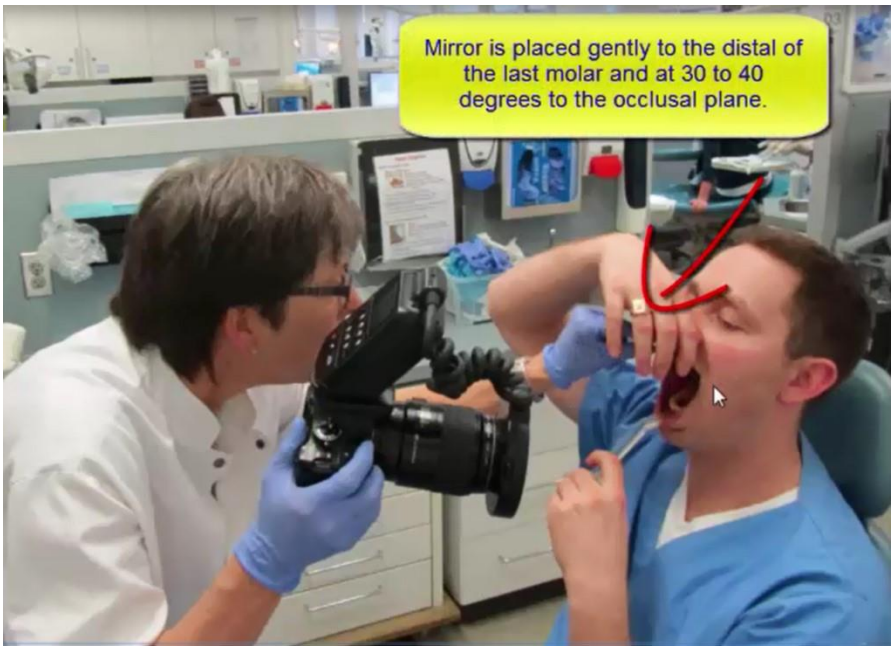
Mandibular Occlusal

Step 6. Ask the technician or participant to retract the mandibular lip away from the teeth.

- Ask the technician or participant to hold the lip retractor as low as possible without any undue pressure to retract the mandibular lip so that the mandibular teeth are visible.

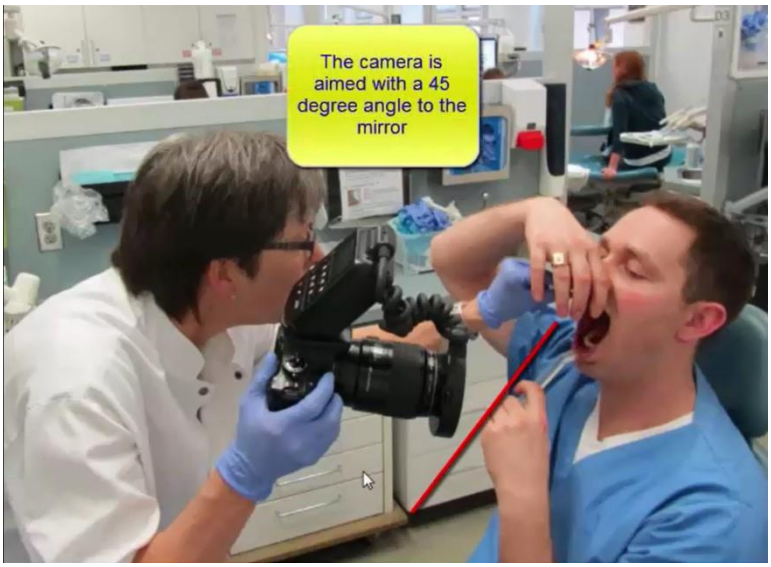
Step 7. Position the occlusal mirror.

- Insert the at a 30 to 40 degree angle to the maxillary teeth.
  - The mirror should be placed gently to the distal of the last molar. ○ Ask the technician or participant to hold the mirror in position. ○ Ask the participant to position their tongue behind the mirror.
  - Ask the participant to open as wide as possible.



Step 8. Position the camera

- Position the camera horizontally.
- Aim camera into the mirror at a 45 degree angle.



Step 9. Take mandibular occlusal photograph and check the image quality; retake if necessary.

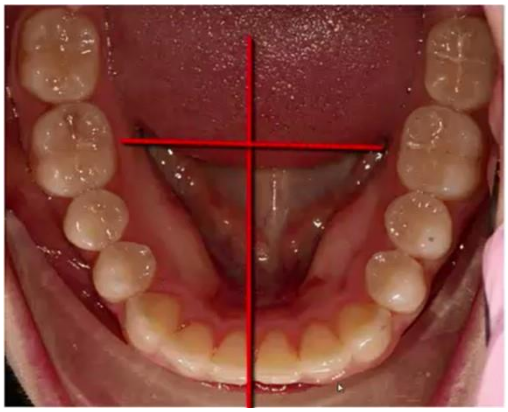
Correct Mandibular Occlusal Intraoral Photographs

All mandibular intraoral photographs should meet the following criteria:

- The entire arch should be visible in the photo.
- The image is parallel to the occlusal plane.
- The arch is centered in the photo.

- The tongue does not interfere with the photo.
- The edge of the mirror does not interfere with the photo.
- All incisors are normal shape and appear properly aligned
- No fog or water spots visible in the photo.
- No shadow at the posterior area of the photo.

Example:



Common Mandibular Occlusal Intraoral Photographs Errors include:

- Aiming camera straight at teeth without mirror
- All teeth are not present
- Tongue interfering with photo
- Poor angulation

Appendix 1: DICOM De-Identification Process

Double click the icon to open file.

DICOM
De-Identification Proc

Appendix 2: Image uploads

The Rare Clinical Diseases Research Network (RDCRN) Image Data Transfer Policy states that all data files (i.e. clinical, laboratory and image) must be collected for long-term storage at the

Data Management and Coordinating Center (DMCC). The study team will upload the images via the RDCRN Members' Website. Prior to uploading, image files are redacted of all patientidentifying information (i.e. name, identifying ID numbers, birth date, sex, ethnicity, medical history, home address, physician's information, etc.) or document corresponding consent and IRB approval in cases where this information cannot be removed.

Save the file using the file naming convention for uploaded images recommended by the RDCRN:

[Participant ID]_[visit]_[image number].[file extension] Where:

- [Participant ID] is the six-digit code assigned by the DMCC system
- [visit] is the corresponding visit as indicated in the protocol (e.g. Baseline, 6 months, 2 years)
- [image number] is a counter for the number of images for that visit for the participant
- [file extension] is the appropriate extension for that file type (e.g. .jpg, .tif, other)

The process for uploading small image files (>100Mb) to the DMCC is as follows:

1. Navigate to the Participant Details page within the Protocol Manager application on the RDCRN Members' website.
2. Select the image upload module.
3. Select the image stored on the study centers' secure network.

For larger files, the DMCC is able to configure a secure FTP (sFTP) folder for the transmission of images. Contact the DMCC to configure the sFTP.

For very large individual files or bath files, physical media (CD, DVD, or hard drive) should be send files to the DMCC.