Effectiveness of Children Experiencing Nitrous Oxide/Oxygen Inhalation Sedation at an Assessment Visit Before Having Treatment.

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The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

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Dedication

This research project is dedicated to my parents for their endless support and encouragement throughout my years of study.

Abstract

Title: Effectiveness of children experiencing nitrous oxide/oxygen inhalation sedation at an assessment visit before having treatment.

Background: Dental anxiety is a common problem, affecting people of all ages, but predominantly children and adolescents. Inhalation sedation (IHS) using nitrous oxide/oxygen (N_2O/O_2) mixture is a pharmacological behaviour management technique that is widely used to manage dental anxiety in children. It is suggested that the use of an acclimatisation would increase the acceptability and the efficacy of N_2O/O_2 success. Even though the introductory appointment has been widely proposed, there have not been any studies conducted to measure the effectiveness of this appointment in improving the success of N_2O/O_2 sedation in children.

Aims: This study aimed to investigate the effect of experience of nitrous oxide/oxygen sedation at assessment prior to dental inhalation sedation on children's anxiety.

Methods: The study was a parallel randomised non blinded control clinical trial. Children aged five to fifteen years who were seen at the Leeds Dental Institute for dental treatment under inhalation sedation were recruited on the assessment appointment (1st visit). Both two groups received an assessment appointment, however participants of the study group tried on the mask and the nitrous oxide/oxygen sedation while the ones of the control group tried on the mask without the nitrous oxide/oxygen sedation. Following the assessment appointment, both groups received a second appointment for treatment. Dental anxiety was measured through two different methods. Primarily through the $MCDAS_f$ questionnaire, which was completed once at the beginning of the assessment visit and twice at the beginning and end of the treatment visit. Secondarily anxiety was measured though the E4 wristband which participants of both groups wore throughout both appointments and recorded their Heart Rate (HR) and Skin Temperature (ST). At the end of the treatment visit, participants and their parents/legal guardians were asked to complete a feedback questionnaire related to the E4 wristband and the experience of N_2O/O_2 sedation at the assessment visit.

Results: Twenty participants were included in the analysis. The control and study groups consisted of 9 and 11 participants respectively with a mean age of 10.35 years. There was no statistically significant difference in the difference of the $MCDAS_f$ score from the first to the second visit between the two groups. Therefore, our null hypothesis was not rejected. No statistically significant differences were found on children's dental anxiety levels before and after the treatment session, on the level of acceptance and completion of treatment and on children's physiological changes between the assessment to the treatment visit between the groups. There were statistically significant reductions of the dental anxiety score of the control group and behavioural score of the study group between the two visits. There was also a minor increase of the mean heart rate of the study group from the assessment to the treatment visit.

Conclusion: There was no significant difference in the level of dental anxiety between the children that experience N_2O/O_2 sedation at the assessment visit with those children that do not and therefore the the null hypothesis, was accepted.

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Chapter 1 Literature Review

1.1 Definitions of fear, anxiety and phobia

Dental anxiety is described in the literature as a common problem, affecting people of all ages, but predominantly children and adolescents (Locker et al., 1999; Locker et al., 2001; Tickle et al., 2009). Dental anxiety, dental fear and dental phobia are words which are commonly used in the literature interchangeably, however there are some important differences (Kleinhauz et al., 1986). Dental fear is outlined as an unpleasant emotional reaction to one or more specific threatening stimuli within the dental situation and is considered as normal (Klingberg and Broberg, 2007). Dental anxiety is described as a state of apprehension that something dreadful is going to happen in relation to dental treatment (Klingberg and Broberg, 2007). Dental phobia is defined as a persistent and excessive fear of dental stimuli and procedures and is regarded as a mental disorder usually resulting in avoidance or substantial emotional distress (Armfield et al., 2013). In the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5, dental phobia is classified as a specific-phobia and, more precisely, under the blood-injection-injury (BII) phobia type (American Psychiatric Association, 2013). However, the above classification has been called into question because of several distinctions between those with dental phobias and other BII phobias (Seligman et al., 2017). Dental fear is considered as developmentally appropriate in young children. However, when the above normal fear transforms to dental anxiety or dental phobia, the resulting avoidance may have a negative effect on a child's health status (Seligman et al., 2017).

1.2 Types of anxiety

Anxiety is frequently categorised as being either state (acute) anxiety or trait (chronic) anxiety (Spielberger, 1972). State anxiety represents the psychological and physiological temporary reactions which are paired with unpleasant situations in a specific time. In contrast, the term trait anxiety refers to a personality trait, describing individual differences related to a tendency to present state anxiety. Trait anxiety is, therefore, relatively stable

over time (Vagg et al., 1980). Dental anxiety is regarded as a form of state anxiety as it develops due to the procedure of dental treatment and is related with negative expectations.

1.3 Aetiology of dental anxiety

The aetiology of dental anxiety is regarded as multifactorial and is still not completely understood (Townend et al., 2000; Klinberg, 2008). Perception of a painful previous dental treatment (Taani, 2001) is related to the development of dental anxiety and is regarded as one of the main factors. Osternick et al., (2008) and Humphris and King (2011), similarly concluded that previous unpleasant experiences within the dental setting are significantly associated with the development of dental anxiety. Specific dental stimuli have been found to be more fear provoking for young dental anxious patients, including the sight, sensation and fear of pain from the needle and dental drill (Rantavuori et al., 2004; Taani et al., 2005).

It has been well documented that negative attitudes in the family environment (Cohen et al., 1982) seem to increase the anxiety and specifically, parental dental fear has a strong correlation with that of the child (Arnrup et al., 2002; Klingberg et al., 2007). The above applies to children who are eight years of age or younger since in children older than eight years, the relationship is less clear (Themessl-Huber et al., 2010).

Rachman (1977) proposed that fears are developed through one or a combination of the following learning pathways: direct conditioning, vicarious learning, and negative information.

Direct conditioning: Direct conditioning is a principal contributing factor of dental anxiety. More specifically, the development of dental anxiety through the mechanism of direct conditioning is regarded as the aetiology in 68% of dentally anxious patients (Berggren et al., 1984).

According to the theory of conditioning by Pavlov, a conditioned stimulus (e.g., the sound of a dental drill) is paired with an unconditioned stimulus (e.g., pain) (Davey, 1989) resulting in the person showing a conditioned response (i.e. anxiety), when confronted with a similar sound (Oosternik et

al., 2009). In simple terms unharmful things are connected with those that have caused the pain (De-Jongh et al., 1995). However, several investigators have found that several adults who have severe fears or phobias cannot recall any certain learning incident (McNally and Steketee, 1985; Menzies and Clarke, 1995) and many individuals with a history of traumatic experiences do not appear to have any anxiety disorders (Poulton and Menzies, 2002).

Vicarious learning: This process describes how feelings of anxiety are acquired through observation of family members, peers and role models displaying anxious behaviours (Hofmann et al., 2008). Vicarious learning has been claimed as the cause of dental anxiety in 12% of dentally anxious patients (Ost and Hugdhal, 1985).

Negative information: This process describes the development of fear from situations and objects that have not been personally experienced due to negative information about a stimulus (Field et al., 2001). More specifically, negative information may increase beliefs about the danger posed by a particular stimulus leading to a fear reaction during a future interaction with the stimulus (Muris et al., 2003). However not all individuals with high levels of dental anxiety report previous unpleasant dental experiences (De jong et al., 2006).

1.4 Anxiety characteristics

Several studies have indicated that there are differences in the characteristics between dentally anxious and non-anxious people (Armfield et al., 2006). There is conflicting evidence in the literature regarding the effect of gender in the development of dental anxiety. Peretz and Efrat (2000) who examined dental anxiety among young adolescent patients concluded that girls were more anxious than boys while Buchanan and Niven (2002) did not find any significant differences between them.

Furthermore, the relationship between anxiety and socio-economic status has been examined. Moore et al. (1993) concluded that both low education and low income appear to increase the risk for moderate dental anxiety; however these variables were not significantly related to higher dental

anxiety. Armfield et al. (2006) conducted a study to assess the relationship between the previously mentioned variables and the prevalence of dental fear. The results indicated that the prevalence of dental fear was higher in women and in people of low socioeconomic status. Research has also shown that younger individuals are more prone to experiencing dental anxiety than middle-aged and elderly adults (Schuller et al., 2003; Armfield et al., 2007).

1.5 Prevalence of dental anxiety

Dental Anxiety is a public health problem affecting a significant percentage of the population. Multiple studies have been conducted worldwide to measure the prevalence of dental anxiety across diverse cultures. In fact, the prevalence rate estimates of dental anxiety vary considerably from 4% to 30 % in different populations and studies (Milica et al., 2015). The variability is attributed to differences in examination methods for dental anxiety (Armfield, 2010) and the threshold anxiety score (cut off) in addition to the influence of the surrounding environmental (Folayan et al., 2004) and cultural factors (Paryab et al., 2010) among the sample populations.

1.5.1 Prevalence of anxiety in adults

Dental anxiety is prevalent in Britain, with 1 in 10 individuals being highly dentally anxious (McGrath and Bedi, 2004). Locker et al. (1999) estimated the prevalence of dental anxiety in a group of young people in Dunedin (New Zealand) to be 16.4 % while 12.5% of their sample of 18-year old’s reported moderate to severe dental anxiety (Locker et al., 2001). A similar figure of 16.1% was reported in Australia including reports of high anxiety from both children and adults (Armfield et al., 2006). In Germany the prevalence of dental treatment fear is estimated at 11% (Enkling et al., 2006) just a bit higher than Norway where the estimation is 10% (Armfield, 2013). Several studies have reported a decrease of fear and anxiety with increasing age while other studies have not established correlation between age and anxiety (Holtzman et al., 1997; Hmud and Walsh, 2009).

1.5.2 Prevalence of anxiety in children

Estimates of childhood dental anxiety have been found to vary from 3 to 43 % in different populations worldwide (Folayan et al., 2004). Dental anxiety is regarded as being common with an estimated prevalence between 6% and 20% in children aged 4 to 18 years old (Klingberg et al., 2007). Just under 50% of children report low to moderate general dental anxiety and between 10% and 20% report high levels of dental anxiety (e.g., dental phobia) (Taani et al., 2005; Dogan et al., 2009). Investigations in The Netherlands and Scotland found similar results with 6% (ten Berge et al., 2002) and 7.1% (Bedi et al., 1992) of youth respectively, reporting high dental anxiety. The figure of dental anxiety in USA was reported at 10.5% by Morgan et al. 1980.

1.6 Anxiety measurements

There are no clear accepted diagnostic criteria available which outline what is a normal or abnormal level of fear experienced in dental settings (Prins, 1994).

Anxiety can be measured with three different methods:

1. “Behavioural assessment”, in which both the emotional and behavioural reactions of the patient during treatment are assessed by the dental team or independent researchers.
2. “Psychometric assessment”, in which the children or parents complete a questionnaire (usually prior to the treatments) indicative of the anxiety levels concerning a variety of dental situations. This method is the most commonly used for the assessment of dental fear and anxiety during childhood and adolescence (Porrit et al., 2013).
3. “Physiological response analysis”, in which variable parameters that are associated with increased anxiety are measured, including salivary cortisol levels (Porrit et al., 2013), patients’ muscle tension when sitting in the dental chair (Holtzman et al., 1997) and pulse rate. An increased pulse rate indicates an increase in adrenergic activity caused by anxiety (Benjiamins, 1995).

1.6.1 Psychometric assessment

1.6.1.1 Children`s Fear Survey Schedule (CFSS) and Dental Subscale of the Children`s Fear Survey Schedule (CFSS-DS)

The Children`s Fear Survey Schedule (CFSS) consists of 80 items on a five-point Likert-scale. The Dental Subscale of the Children`s Fear Survey Schedule (CFSS-DS) was later developed which is a shorter version consisting of 15 items, each scored from 1 (not afraid) to 5 (very afraid). Scores over 38 are suggestive of severe dental fear (Newton and Buck, 2000) whilst scores below 32 are regarded as non-clinical fear (Versloot et al., 2008).

1.6.1.2 Corah`s Dental Anxiety Survey (CDAS) and Modified Dental Anxiety Survey (MDAS)

In 1969, Corah developed the Corah's Dental Anxiety Survey (CDAS) - a four-item scale. It measures patients' reactions within four different dental treatment settings: before attending the dental surgery, waiting in the dentists' office, sitting in the dental chair and undergoing treatment. Each question has five possible answers assessed on a scale from 1 to 5. 1 indicates no anxiety whereas 5 indicates the maximum level of anxiety. Therefore, the CDAS score can range from 4 (no anxiety) to 20 (extreme high anxiety) (Corah, 1969). CDAS is a very popular research tool for measuring dental anxiety in adults worldwide. It is highly reliable and can be efficiently completed in the clinical setting in less than five minutes (Guinot et al., 2011). However, it does not assess anxiety related to local or general anaesthesia, or inhalation sedation (Wong et al., 1998). Since the CDAS was developed mainly for use in the adult population, the design of the CDAS may not be suitable for children (Porritt et al., 2013).

The MDAS is the modified version of CDAS which has an extra question regarding local anaesthetic, due to the fact that injection is an anxiety provoking stimulus for many individuals. The MDAS also includes modifications in the answer options to reflect anxiety in a clearer order. The total score is the sum of all 5 items which ranges from 5 to 25. Nineteen and above is the cut-off value that indicates a high level of anxiety (Humphris et

al., 1995). Although the MDAS did address some of the issues with the DAS, it was still developed using adult subjects.

1.6.1.3 Modified Child Dental Anxiety Scale (MCDAS) and faces version of the Modified Child Dental Anxiety Scale ($MCDAS_f$)

MCDAS has been developed by Wong and Humphris based on the concept of CDAS (Wong and Humphris, 1998). The MCDAS is an eight-item scale; seven items ask about a child's anxiety in specific situations related to visiting the dentist (e.g., “having your teeth looked at,” “having a tooth taken out,” “being put to sleep to have treatment”, “ having a “gas-air” mixture given to you that will make you feel comfortable, but will not make you sleep for treatment”), while one item asks about overall feelings about going to the dentist (“going to the dentist generally”) (Wong et al., 1998). The scale has a good test-retest reliability and internal consistency (0.84) (Howard and Freeman, 2007). It has been effectively used in children aged eight years and older (Howard and Freeman, 2007; Buchanan, 2010).

Howard and Freeman (2007) further modified the MCDAS by adding 5 smiley faces ($MCDAS_f$) to make it suitable for younger children and children with cognitive disabilities (Howard and Freeman, 2007). The faces version of the MCDAS has been tested in a series of studies of younger children between five and ten years of age (Howard and Freeman, 2007). Compared to the 15-item CFSS-DS, the $MCDAS_f$ has the advantage of being shorter and therefore faster to complete (Howard and Freeman, 2007).

1.6.1.4 Venham picture test (VPT)

The Venham picture test (VPT) was developed in 1977 and consists of eight pairs of pictures each of which shows two pictures portraying opposite feelings (Sonnenberg and Venham, 1977). It is usually employed for very young children, in order to avoid the need for extensive oral communication (Buchanan and Niven, 2002). The final score is the total of the number of times the child selects the high-fear stimulus (the minimum score is zero whereas the maximum is eight). The VPT has shown many advantages when used in research; it is simple, quick to use and suitable for use with children 2-8 years of age (Foster and Park, 2012). However, it does not effectively differentiate between anxious and non-anxious children since no

parameters were set to indicate high levels of anxiety (Buchanan and Niven, 2002).

1.6.1.5 Smiley Faces Program (SFP)

The Smiley Faces Program is a 4-item computerised scale consisting of different face expressions which aim to describe the child's response to a variety of dental interventions. At first, a face which is neutral is presented to the child followed by the appearance of questions on the screen which last for a few seconds during which the child is asked to replace the neutral face with one of seven faces that best describes how they feel about the dental item in question. Even though this method has shown good reliability it is limited by the need for access to computer equipment (Howard and Freeman, 2007).

1.6.1.6 Facial Image Scale (FIS)

The FIS comprises of a row of five "genderless" faces, ranging from very unhappy' to 'very happy' and numbered from 1 to 5. Children are told to select which face they feel represents them at that particular moment. It may be used as a measure by itself, or combined with other measures (Porritt et al., 2013). This measure is suitable for young children and those with limited cognitive development (Porritt et al., 2013). The scale is considered simple and easy to use and takes a short time to be completed (Olumide et al., 2009). It is proven more suitable for very young children around three years of age who lack the cognitive ability to understand and complete written or verbal questionnaires and gives an immediate indication about child anxiety (Buchanan and Niven, 2002).

1.6.2 Physiological response to anxiety

The physiological data that are used for stress monitoring are considered responses of the human autonomous nervous system (ANS) (Carlson 1998). The ANS consists of two components: the parasympathetic nervous system, which controls involuntary resting functions (e.g., activation of this system slows heart rate), and the sympathetic nervous system, which increases in involuntary processes (e.g., heart rate and respiration) (Kemeny 2003). The Autonomic Nervous System response to stress, known as the fight or flight

response, involves the activation of the sympathetic branches and inhibition parasympathetic ones. In other words, there is shunting of blood away from the non-essential organs to essential organs for flight, such as the brain, heart and muscles. This results in the decrease of peripheral skin temperatures and the increase of pulse and respiratory rates.

1.6.2.1 Anxiety and Heart Rate

During a period of anxiety, physical and autonomic changes occur. Therefore, it is reasonable to assume that measuring the function of the autonomic nervous system is a useful tool for measuring psychological states (Shinba et al., 2008). The activation of the sympathetic system increases the heart rate and cardiac contractibility (Franchini and Cowley 2011). Heart rate (HR) is a measure of the number of beats per minute. Anxiety is associated with an increased HR (Noteboom et al., 2001).

1.6.2.2 Anxiety and Skin Temperature

Skin temperature (ST) refers to the temperature measured on the surface of the human skin (Taj eldin et al., 2018). When individuals experience anxiety, their sympathetic nervous system is activated. Blood volume is shifted away from digestive organs and skin toward larger skeletal muscles. Since blood moves away from the peripheral surfaces, the skin temperature is lowered (Wardell and Engebretson 2001).

1.6.2.3 E4 wristband to measure physiological parameters

Empatica E4 wristband (Empatica, Milan, Italy) (https://www.empatica.com/research/e4/) (Figure 1) is a wrist-worn wireless multi-sensor devise capable of measuring parameters such as electrodermal activity (EDA), heart rate, motion-based activity, and skin temperature over time. The wristband includes an EDA sensor, a photoplethysmograph (PPG) for the heart rate, 3-axis accelerometer for movements, and an optical infrared thermometer for detecting the skin temperature (Cabibihan et al., 2016). The E4 wristband is a CE marked medical device and is intended for research (Regalia et al., 2019). It has been used in several studies and has shown high validity (McCarthy et al., 2016; Ollander et al., 2016; Onorati et al., 2017; Rudovic et al., 2018; Siirtola et al., 2018;).

Figure 1 E4 wristband-Empatica, reproduced with permission

1.7 Anxiety complications

Research has shown that there is an association between childhood dental anxiety and an increased number of decayed and extracted teeth, episodes of toothache and symptomatic attendance, and lower oral health-related quality of life (Wogelius et al., 2005; Nuttall et al., 2008; Luoto et al., 2009). Clinicians' stress is also increased while treating anxious patients (Moore and Brodsgaard, 2001) along with the duration of the treatments and inevitably the costs (Rafique et al. 2008). Dental anxiety is strongly associated with behaviour management problems (Klingberg et al., 1995; Wogelius et al., 2003; Kyritsi et al., 2009; Gustafsson et al., 2010; Salem et al., 2012).

1.8 Children's behaviour clinical classification

Children can be classified into four categories according to their behaviour (Welbury et al., 2018):

1. Cooperative children.
2. Potentially cooperative children that may manage simple procedures, but more complicated operations may be beyond their coping ability.
3. Pre-cooperative children that lack cooperative ability but may potentially cooperate later after reaching a higher level of maturation.
4. Uncooperative children who cannot cope with any procedure due to their high anxiety levels.

For children who are cooperative or potentially cooperative, non-pharmacological methods of behaviour management may be a suitable method of anxiety control; however, pre-cooperative and uncooperative children require a different approach, which may include conscious sedation or general anaesthesia in order to reduce anxiety and facilitate the delivery of dental treatment (Welbury et al., 2018).

1.9 Conscious sedation

The General Dental Council (GDC, 1997) and the Royal College of Anaesthetists (RCA) have both encouraged the use of conscious sedation as a safe alternative to general anaesthesia for dental care. Conscious sedation is regarded as a viable and cost-effective alternative to general anaesthesia for children requiring extractions, especially orthodontic extractions (Holroyd, 2008) while in a review conducted by Lyratzopoulos and Blain, it was reported that morbidity associated with inhalation sedation is minor and infrequent when compared to general anaesthesia (Lyratzopoulos and Blain, 2003).

In the UK, according to the report of the Intercollegiate Advisory Committee for Sedation in Dentistry in 2015, conscious sedation is defined as: ”*a technique in which the use of a drug or drugs produces a state of depression of the central nervous system enabling treatment to be carried out, but during which verbal contact with the patient is maintained throughout the period of sedation. The drugs and techniques used to provide conscious sedation for dental treatment should carry a margin of safety wide enough to render loss of consciousness unlikely.”* Furthermore “*The level of sedation must be such that the patient remains conscious, retains protective reflexes, and is able to understand and to respond to verbal commands” (*GDC 1997), “*either alone or accompanied by a light tactile stimulus” (*SDCEP 2017). In any case where these criteria are not fulfilled and a state of ‘deep sedation’ occurs, this must be considered as a case of general anaesthesia (GDC 1997).

The routes of administration of sedative drugs used in clinical paediatric dentistry are oral, inhalation, intravenous (IV), and trans-mucosal (e.g. nasal, rectal, and sublingual) (Welbury et al., 2018). The standard techniques of conscious sedation in the UK are inhalation sedation, using nitrous oxide and oxygen and IV sedation with a single benzodiazepine drug, usually midazolam. Both are considered effective and adequate for the majority of patients (BDA 2011). Where conscious sedation is indicated it should be regarded as an adjunct to, rather than a substitute for, good behaviour management techniques (BDA 2011).

1.10 Inhalation sedation

Inhalation sedation (IHS) with a mixture of nitrous oxide and oxygen is the first choice for young patients who are unable to tolerate dental treatment with local anaesthesia alone and who have a sufficient ability to communicate (SDCEP 2017). The technique uses sub-anaesthetic concentrations of nitrous oxide delivered with oxygen in a titratable dose from dedicated equipment via a nasal mask (Holroyd, 2008). It's ease of administration, wide margin of safety, analgesic and anxiolytic effects in combination with its rapid reversibility, have rendered it an ideal drug, very suitable for use in children (Paterson and Tahmassebi, 2003; Houpt, 2004). The American Academy of Paediatric Dentistry (AAPD) also recognises nitrous oxide/oxygen inhalation as a safe and effective technique to reduce anxiety, produce analgesia, and enhance effective communication between a patient and health care provider.

1.10.1 Pharmacology of nitrous oxide

Nitrous Oxide (N_2O) is a colourless, virtually odourless gas with a faintly sweet smell and is slightly heavier than air with a specific gravity of 1.53 (Girdler and Hill, 1998; Paterson and Tahmassebi, 2003; Becker and Rosenberg, 2008). On inhalation of N_2O, it has a rapid uptake in the lungs as it is quickly absorbed from the alveoli and is held in a simple solution in the blood serum. The alveolar concentration rapidly approaches the inspired concentration. The relative insolubility of the N_2O in the alveoli results in its passage to the low-pressure gradient areas of the body such as Central

Nervous System (CNS) (Clark and Brunick, 2008). The low tissue solubility and high minimum alveolar concentration (MAC), with a value more than one atmosphere, enable rapid onset of action coupled with a rapid recovery. Once N_2O is no longer being inhaled, N_2O within the Central Nervous System (CNS) will rapidly pass down the gradient into the bloodstream and out of the body via the lungs while a very small amount is eliminated in body fluids (Paterson and Tahmassebi, 2003). The administration of 100% Oxygen (O_2) to the patient for 3-5 minutes once the N_2O has finished is recommended due to the risk of diffusion hypoxia, since N_2O is more soluble in blood than nitrogen (Paterson and Tahmassebi, 2003).

1.10.2 Mechanism of action

Nitrous oxide is a mild sedative agent that causes CNS depression and euphoria. It has a very slight effect on the respiratory system and the protective reflexes of the airway. The cardiac output is minimally depressed whilst peripheral resistance is slightly increased, thus maintaining the blood pressure (Paterson and Tahmassebi, 2003). Nitrous oxide has several mechanisms of action. The analgesic effect of N_2O appears to be initiated by stimulated neuronal release of endogenous opioid peptides, with subsequent activation of opioid receptors and descending gamma-amino-butyric acid (GABA) and noradrenergic pathways that modify nociceptive processing at the spinal level (Emmanouil et al., 2007). When administered before intraoral injections in dentistry, N_2O has the ability of elevate the patient's pain threshold (Malamed, 2018). However, the degree of analgesia is quite variable from patient to patient and therefore cannot be relied on to provide all of the pain control required for a procedure (Paterson and Tahmassebi, 2003; Malamed, 2009). The anxiolytic effect involves activation of the GABA receptors either directly or indirectly through the benzodiazepine binding sites (Emmanouil et al., 2007).

1.10.3 Advantages of nitrous oxide/oxygen inhalation technique

The nitrous oxide/oxygen inhalation technique is a non-invasive technique (Paterson and Tahmassebi, 2003) with the most rapid onset of action of all sedation techniques (Paterson and Tahmassebi, 2003; Malamed, 2018).

Usually two to three minutes are required for the development of clinical action (Paterson and Tahmassebi, 2003; Malamed, 2018). The recovery time from inhalation sedation is also very rapid and is the most complete of any pharmaco-sedation technique, achieved within five minutes (Paterson and Tahmassebi, 2003; Malamed, 2018). Adult patients may usually be discharged from the dental surgery alone, with no cautions about activities (Malamed, 2018). The IHS technique is based on the titration of the drug, which is the ability to administer small, incremental doses of a drug until a desired clinical action is obtained. The depth of sedation achieved with inhalation sedation may be altered from moment to moment, permitting the drug administrator to increase or decrease the depth of sedation easily. The degree of control represents a significant safety feature of inhalation sedation while it is the only sedation technique that enables such a degree of control over the clinical actions of the drug being used (Paterson and Tahmassebi, 2003; Malamed, 2018). Furthermore, the drug administrator is capable of controlling the duration of action and therefore the planned procedure may be of any length (Malamed, 2018). This is an important advantage over sedation techniques with a relatively fixed duration of clinical activity which the dental treatment must be tailored to meet (Malamed, 2018). Whereas peak clinical effect does not develop in most techniques for a considerable time, inhalation and IV drug administration do provide peak clinical actions in a time span permitting titration. For the IV route, the time-to-peak effect varies with the drug administration ranging from one minute to approximately 20 minutes. On the other hand, the inhalation route has a three to five minute peak action (Malamed, 2018). The drugs used in this technique have no adverse effects on the liver, kidneys, brain, or cardiovascular and respiratory systems (Hosey, 2002; Malamed, 2018). N_2O IHS causes minimal impairment of any reflexes, thus protecting the cough reflex (Paterson and Tahmassebi, 2003) and very few side effects have been associated with the use of nitrous oxide, therefore IHS with this agent is regarded as a safe technique (Malamed, 2018). N_2O does appear to provide analgesic properties when given in the usual sedative concentrations (Hosey, 2002; Malamed, 2009). Certain procedures, such as those involving soft tissues (e.g. scaling), may be performed in many

instances without using local anaesthesia (Paterson and Tahmassebi, 2003; Malamed, 2018). No injections are required for the administration of the drug, although local anaesthesia is still necessary for most dental procedures (Paterson and Tahmassebi, 2003; Malamed, 2018). This is particularly important for needle phobic patients (Paterson and Tahmassebi, 2003).

1.10.4 Disadvantages of nitrous oxide/oxygen inhalation technique

Nitrous oxide as an inhalation agent appears to have lack of potency (Paterson and Tahmassebi, 2003; Malamed, 2018) and is associated with concerns about nitrous oxide pollution and potential occupational health exposure hazards (Paterson and Tahmassebi, 2003). The IHS technique depends significantly on psychological reassurance (Paterson and Tahmassebi, 2003). Patients must be able to breathe through the nose and must be willing to accept the nasal hood (Paterson and Tahmassebi, 2003; Malamed, 2018). The interference of the nasal hood with an injection to anterior maxillary region has also been reported as a disadvantage of the above technique (Paterson and Tahmassebi, 2003).

1.10.5 Adverse effects

Acute and chronic adverse effects of nitrous oxide for the patient are rare (Donaldson and Meechan, 1995). The most common adverse effects, which occur in 0.5-1.2 percent of patients, are nausea and vomiting (Kupietzky et al., 2008; Galeotti et al., 2016). The incidence can be increased by a high concentration of N_2O, long duration of sedation, fluctuations in nitrous oxide levels and a heavy meal prior to administration of nitrous oxide (Paterson and Tahmassebi, 2003; Malamed, 2018; AAPD, 2018). Fasting is not required for children undergoing inhalation sedation using nitrous oxide, but dentists might recommend that a light meal only is consumed in the two hours prior to the appointment (Hosey, 2002). Diffusion hypoxia can occur because of decreased oxygen saturation levels in the blood caused by the rapid elimination of N_2O on its termination (Clark and Brunick, 2008). This may lead to headache, disorientation, and nausea and can be prevented by

delivering 100% oxygen postoperatively for 3-5 minutes (Clark and Brunick, 2008).

1.11 The use of acclimatisation in increasing effectiveness of IHS.

Patient assessment must include a full medical and dental history (Hosey, 2002). Fitness for conscious sedation must also be assessed and usually the classification system introduced by the American Society of Anaesthesiologists (ASA) is implemented for this purpose.

Only patients who are ASA Class I or Class II may be considered candidates for conscious sedation as outpatients. Patients in ASA Class III and Class IV represent special problems and require individual consideration and should be treated in a hospital environment, involving the assistance of medical support where appropriate (Paterson and Tahmassebi, 2003; Hosey, 2002).

Pre-operative assessment has been suggested to be undertaken on a separate day from that of the proposed treatment (Patterson and Tahmassebi, 2003; RCA, 2015; SDCEP, 2017; Malamed, 2018;) and rather than starting the sedation at the first dental visit, many clinicians suggest an acclimatisation/familarisation visit (Patterson and Tahmassebi, 2003; Malamed, 2018) and that a form of psychological preparation may be required (RCA 2015). Therefore, it has been suggested that a short appointment for familarisation and acclimatisation with the technique and the procedure should take place before the actual treatment appointment. At this appointment the dentist can demonstrate and explain N_2O/O_2 equipment as well as answer a patient's questions or concerns related to the upcoming treatment. Furthermore, the operator may try applying the N_2O/O_2 sedation but without performing any treatment or only minimal treatment is carried out such as fissure sealants.

There is controversy regarding the use of acclimatisation visits for dental sedation treatment pathways for children and there have not been any studies to evaluate the effect of acclimatisation on child anxiety and success of completion of treatment under inhalation sedation. It has been suggested that the extra visit may add to the cost and delay treatment.

1.12 Rationale for this study

Even though the introductory appointment has been widely proposed, there have not been any studies conducted to measure the effectiveness of this appointment in improving the success of N_2O/O_2 sedation in children. Such a study would allow the generation of guidelines. The only evidence-based resource that recommended the use of introductory visit was produced by SDCEP in 2017. They issued the following statement: *"A brief trial of nitrous oxide/oxygen at the assessment appointment may be helpful for the psychological preparation of some children"*. However, specific evidence to support this statement was unclear. Therefore, at the present time, the recommendations are based on expert opinion and are not evidence based.

1.13 Aim

To assess the effect of experience of N_2O/O_2 sedation at assessment, prior to dental IHS on children's anxiety.

1.14 Null hypothesis

There are no differences in children's anxiety scores between the children that experience N_2O/O_2 sedation at the assessment visit with those children that do not.

1.15 Outcome measures

1.15.1 Primary outcome

Effect of experience of N_2O/O_2 sedation at the assessment visit measured by the dental anxiety score difference between the beginning of the assessment visit (baseline) and the beginning of the treatment visit.

1.15.2 Secondary outcomes

1. Completion of treatment.
2. Level of acceptance of treatment.

3. Difference in the child dental anxiety level before and after the treatment session.
4. Physiological changes from the assessment to the treatment visit.
5. Patient experience.

Chapter 2 Materials and Methods

2.1. Introduction

The study was a parallel randomised non blinded control clinical trial. Ethical approval was obtained from the Northwest - Greater Manchester East Research Ethics Committee (REC reference number20/NW/0157) (Appendix A). Appropriate approval from the Leeds Research and Innovation Department was also granted so that the research could take place at the Leeds Teaching Hospital Trust (R&I No: DT20/136112).

Patients were recruited at the Leeds Dental Institute on the assessment appointment (1st visit). On the assessment day, information sheets (Appendix B, C, D) and the procedures were explained in detail to parents and children in simplified language and questions were answered as well as informed consent/assent (Appendix E, F) was explained and the forms signed by those who met the eligibility criteria. All the above procedures were performed by the Lead Researcher.

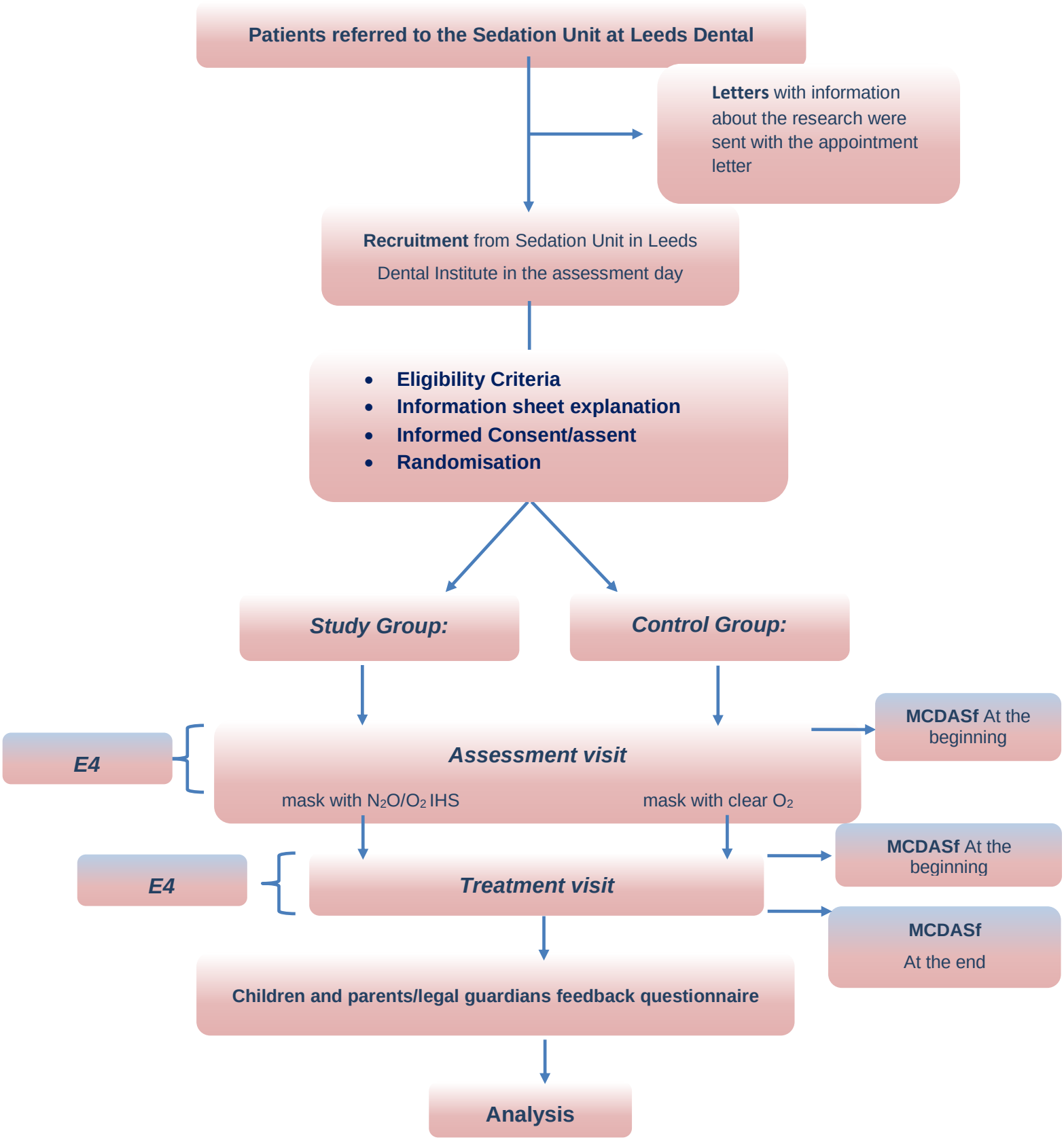
Both groups received an assessment appointment. Patients who had been randomly assigned to the study group tried on the mask with N_2O/O_2 sedation while those assigned to the control group tried on the mask with O_2 only. Following the assessment appointment, both groups received a second appointment for treatment. The clinician for both assessment and first treatment session was the same for all participants of both groups and was the Lead Researcher.

The $MCDAS_f$ questionnaire (Appendix G) was completed by participants at the beginning of the assessment visit to measure their anxiety. Participants wore the E4 wristband throughout this appointment which recorded their heart rate and skin temperature (Appendix I).

At the beginning of the treatment visit the $MCDAS_f$ was completed again both at the beginning and at the end of the visit. Patients also wore the E4 wristband throughout this appointment. At the end of the treatment visit, the participants and their parents/legal guardians were asked to complete a feedback questionnaire (Appendix J, K, L, M) related to the E4 wristband and the experience of N_2O/O_2 sedation at the assessment visit.

The research took place in a side surgery of the Sedation Unit in the Leeds Dental Institute. Demographic data such as age, gender, behavioural score and if the treatment was completed, were collected from the patient's dental notes (Appendix H). Each stage will now be considered in detail.

2.2. Study flow chart



2.3. Sample size

Statistical advice was sought for the sample size calculation. According to the pilot study design we aimed for 30 participants in each group (Lancaster et al., 2004) therefore 60 participants in total were recommended to be enrolled in this study. To account for an estimated 10% loss from first to second visit, we planned to enrol 68 participants in total.

2.4. Eligibility criteria for participants and groups

The potential participants were identified from the inhalation sedation waiting list. Potential participants received information sheets (age tailored) about the study through the post, with the first assessment appointment for IHS sedation, at least two weeks before the sedation assessment visit. On the assessment day, information sheets were provided as well as an explanation of the procedures to both children and parents/legal guardians and any queries or questions were answered. The informed consent/assent was also explained and forms were signed by those who meet the eligibility criteria and agreed to take party in the study. The parent or legal guardian was asked to sign a consent form while children completed an assent form. For patients who did not meet the eligibility criteria or did not want to participate in the study, a regular appointment for sedation and treatment was given.

2.4.1 Inclusion Criteria:

- Patients attending the Sedation Unit for dental treatment under inhalation sedation.
- Children aged 5 to 15 years.
- ASA Class I or II.
- First time having inhalation sedation.

2.4.2 Exclusion Criteria:

- Participants who refuse to wear the mask.
- Language barriers where no interpreter was available
- Parents/Carer who refused to sign consent or children who did not assent.

2.4.3 Control and Study groups:

Participants assigned to the study group received assessment with experience of N_2O/O_2 sedation. Participants assigned to the control group received assessment without experience N_2O/O_2 sedation and they tried the mask with O_2 only.

2.5. Patient and Public Involvement

Development of the research question and outcome measures were informed by patients' priorities, experience, and preferences. Before the study was started, a survey on the preference for the use of N_2O/O_2 sedation at an assessment visit assessment prior to the treatment visit was carried out, with 10 children (5 boys and 5 girls), aged 5-15 years after the end of one of their treatment visits. We discussed the randomisation with the children and their parents to see if they would be happy to be randomised to either receiving the sedation or oxygen only at the assessment visit. As part of the above survey, we also asked children how they would feel completing an $MCDAS_f$ (anxiety form) and showed them the E4 watch and placed it on their wrists and asked them if they would be happy to wear the watch throughout the treatment. The questionnaires were explained and answered by the children and their parents.

Nine out of ten children and their parents reported that they would agree to take part in the study, and they would be happy to be randomised. One 13 year-old girl mentioned that she would not agree to take part because she would not like to be randomised as she would prefer to try on the mask and the relaxation gas at the first appointment to see how it felt like before the treatment. Her mother agreed. All the children stated that they would be happy to complete the $MCDAS_f$ form. The completion of the form on the assessment visit had already been implemented in the Sedation Unit at Leeds Dental Institute. Therefore, patients were already familiar with the form.

Nine out of the ten children tried the E4 watch for 5 minutes and said that it was comfortable and could wear it throughout each appointment. One 9 year

old boy did not want to try the wristband. The E4 watch was disinfected with antibacterial wipes in between the patients for cross infection control.

As far as the questionnaire was concerned, following patients' feedback, smiley faces were added underneath each answer and the last question was modified from "*Is it a good idea to try on the nose piece and the magic gas on the first visit or not*" to "*Is it a good idea to try on the nose piece and the magic gas* ***before treatment*** *on the first visit or not*".

2.6. Informed consent and assent

Parents or legal guardians were asked by the Lead researcher who had been trained and had comprehensive knowledge about the study, to sign a written consent form (Appendix E) before enrolling their child into the research. Consent was only asked from the parent/legal guardian after confirming that they fully comprehended the intentions of the research and had considered all possible consequences of their child's involvement in the research. An age-appropriate information sheet (Appendix C,D) and assent (Appendix F) form were given to the participating child. Participants had the chance to ask for more details.

2.7. Randomisation: method and procedure

After recruitment was completed, eligible participants were assigned randomly to either having an assessment visit with experience of N_2O/O_2 sedation or an assessment visit with experience of O_2 only before the treatment session. After the explanation of the information sheets and the procedures and the signing of the consent form, patients who agreed to take part were randomised. The randomisation was performed by an external independent person using an online random number generator (Random.org) where 0 accounted for control group (assessment without experience of N_2O/O_2 sedation) and 1 for study group (assessment with experience of N_2O/O_2 sedation). The generated list was kept by the Lead Researcher. Following the sequence of the list, patients were randomly allocated to one of the two groups according to their appointment sequence.

2.8. Assessment visit:

2.8.1 Study group

Participants that were assigned to the study group tried the mask with N_2O/O_2 inhalation sedation on the assessment visit. Prophylaxis was performed on that visit. The $MCDAS_f$ was completed at the beginning of the visit. The participants wore the E4 wristband throughout the appointment.

2.8.2 Control group

Participants that were assigned to the control group tried the mask with O_2 only. Prophylaxis was performed on that visit. The $MCDAS_f$ was completed at the beginning of the visit. The participants wore the E4 wristband throughout the appointment.

2.9. Treatment visit:

On the treatment visit, for both groups, treatment was performed under N_2O/O_2 IHS. The $MCDAS_f$ was completed at the beginning and at the end of the visit. The participants wore the E4 wristband throughout the appointment. The feedback questionnaire was completed by the participants (Appendix J,K) and their legal guardians (Appendix L,M) at the end of the appointment.

Each participant was given a battery charged toothbrush at the end of the treatment session as a modest acknowledgement of their time and any inconvenience associated with the study.

2.10. Inhalation sedation technique

The unit in which the sedation took place is shown in Figure 2. Apart from the Lead researcher, a dental nurse assisted with the dental treatment on every appointment. A specially trained sedation nurse was responsible for the monitoring during sedation. The Porter Brown inhalation sedation machine (RA Services, Keighly, W. Yorkshire, UK) was used. Once the appropriate nasal hood was selected, 100% O_2 was introduced for 1-2 minutes. Following that, the level of N_2O was increased in 10% increments until signs of sedation were observed. The endpoint was between 30–40%

nitrous oxide. For the participants of the study group, the same percentage was used in both visits.

Figure 2 Sedation unit

2.11. E4 wristband data

After each appointment, the acquired data were uploaded by the Lead Researcher to the Empatica cloud by first plugging the E4 wristband into the University computer via USB. The Empatica Manager, which is a desktop memory sync program, operates automatically as soon as the user has logged in and connected the E4 wristband. Data upload is secure and does not include any personally identifying information. Following that, the sessions that were associated to the Lead Researcher account were accessed and reviewed through the Empatica Connect web platform. Data from each session were visualised and downloaded in timestamped Comma Separated Values (CSV) format.

2.12. Primary outcome

- *Effect of experience of N_2O/O_2 sedation at the assessment visit measured by the dental anxiety score difference between the beginning of the assessment visit (baseline) and the beginning of the treatment visit.*

The $MCDAS_f$ (Figure 3) was used to assess the dental anxiety scores at the beginning of the assessment visit (baseline score) and at the beginning of the treatment visit. The two recorded scores were compared. Children above the age of eight years completed the questionnaire without assistance while for younger children, the questions were read out and the children pointed to the appropriate face on the scale to indicate their level of anxiety as recommended by Howard and Freeman, 2007.

For the next eight questions I would like you to show me how relaxed or worried you get about the dentist and what happens at the dentist. To show me how relaxed or worried you feel, please use the simple scale below. The scale is just like a ruler going from 1 which would show that you are relaxed, to 5 which would show that you are very worried.

1 would mean : relaxed / not worried
2 would mean : very slightly worried
3 would mean : fairly worried
4 would mean : worried a lot
5 would mean : very worried

How do you feel about …					
… going to the dentist generally?	1	2	3	4	5
… having your teeth looked at?	1	2	3	4	5
… having your teeth scraped and polished?	1	2	3	4	5
… having an injection in the gum?	1	2	3	4	5
… having a filling?	1	2	3	4	5
… having a tooth taken out?	1	2	3	4	5
… being put to sleep to have treatment?	1	2	3	4	5
… having a mixture of 'gas and air' which will help you feel comfortable for treatment but cannot put you to sleep?	1	2	3	4	5

Figure 3 Faces version of the Modified Child Dental Anxiety Scale

2.13. Secondary outcomes

2.13.1 Completion of treatment

At the end of the first treatment visit whether the treatment was completed or not was recorded.

2.13.2 Level of acceptance of treatment

The level of acceptance of treatment was measured using the Houpt Behaviour Rating Scale. At the end of each session, an overall evaluation of the child's behaviour was made according to the Houpt rating scale (Table 1). These ratings were performed by the Lead researcher.

Table 1 Houpt overall behaviour rating scale

Score	Description
1	Aborted: No treatment rendered
2	Poor: Treatment interrupted, only partially completed
3	Fair: Treatment interrupted but eventually completed
4	Good: Difficult but all treatment was preformed
5	Very good: Some limited crying or movement
6	Excellent: No crying or movement

2.13.3 Differences in child dental anxiety levels before and after the treatment session.

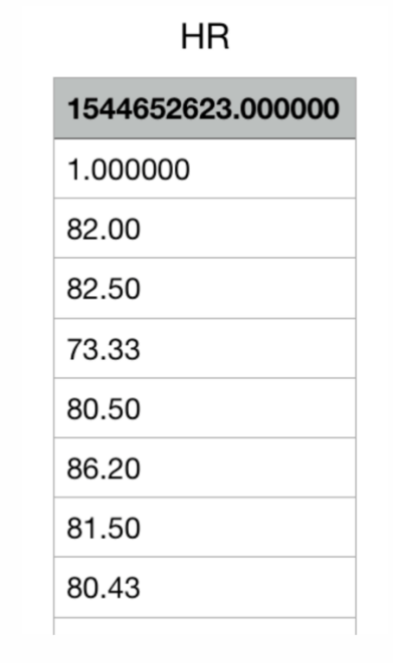
The Lead Researcher assessed the dental anxiety level before and after the treatment session using the $MCDAS_f$ questionnaire.

2.13.4 Physiological changes from the assessment visit to the treatment visit.

The physiological changes were measured in real time by the commercially available Empatica E4 wristband (Empatica, Milan, Italy). Patients of both groups wore the E4 wristband during both assessment and treatment visit. The E4 was placed on the participants' wrists once they had sat on the dental chair and was removed at the end of the appointment. It was placed on the non-dominant hand. It was disinfected between the participants.

The data was stored in the internal memory of the E4 wristband. For the data to be accessed, they must first be downloaded via USB connection in a desktop application which is called "Empatica Manager". Following that, data is uploaded to the Empatica cloud platform and can be accessed through the "Empatica Connect" web application. Data upload is secure and does not include personally identifying information, in compliance with the European Health Insurance Portability and Accountability Act requirements (Garbarino et al., 2014). The E4 Realtime Application is also available for the phone, from where data can be streamed, viewed, and automatically uploaded to the Empatica Connect account after the end of the streaming session.

From the Empatica Connect data, which is organised by sessions that have a start time and duration, can be visualised, downloaded, and then deleted. Data is downloaded in the form of a Comma Separated Values (CSV) file, which is a plain text file that contains a list of data (Garbarino et al., 2014). Figure 4 is an example of a produced HR CSV file which contains the HR measurements.



HR
1544652623.000000
1.000000
82.00
82.50
73.33
80.50
86.20
81.50
80.43

Figure 4 Heart rate CSV file

The first row is the initial time of the session expressed as unix timestamp in UTC. The second row corresponds to the sampling rate which is 1 Hz meaning that the provided values in the file are 1 sec apart from each other. The HR values begin at the third row and continue in the rest of the rows. The data from temperature sensor were expressed in degrees on the Celsius (°C) scale (sampled at 4 Hz) on a similar spreadsheet like the HR.

To compare the physiological measurements between the assessment and the treatment visits, two methods were used. At first, we made a direct comparison of the mean HR and ST between the two visits. Vieluf et al., (2020) also used the mean values of HR and ST obtained from the E4 wristband to record the changes in the ANS in the setting of epileptic seizures. Vieluf et al., (2020) indicated that simple mean signal values may be insufficient. Therefore, we added an additional measurement which is the comparison of the difference between the baseline and highest HR value

between the two visits. Regarding the ST, the difference between the baseline and lowest ST value was compared between the two visits. The baseline was set at 5 minutes according to Milstein and Gordon (2020) research.

2.13.5 Patient experience.

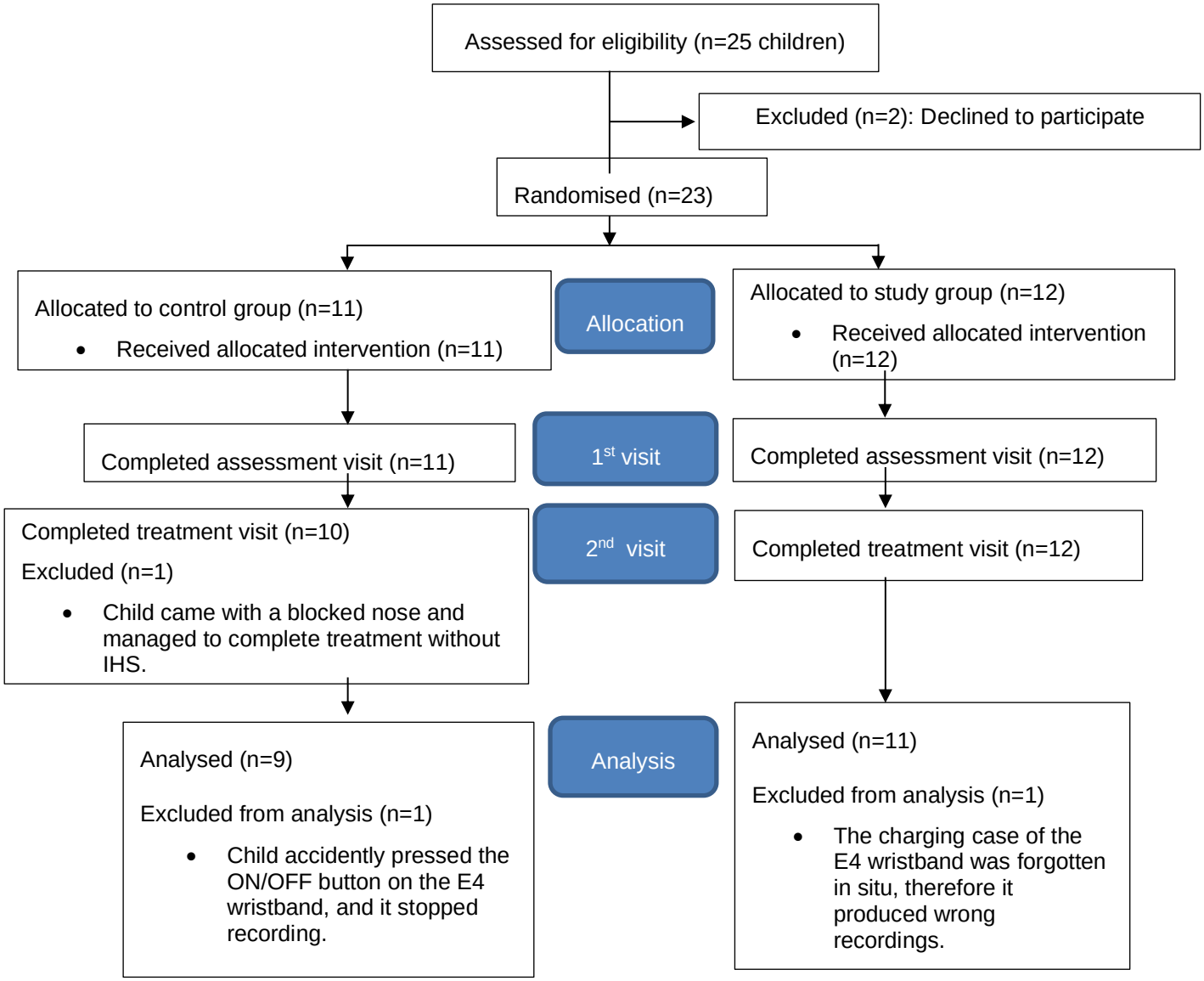
Feedback about the experience of N_2O/O_2 sedation at the assessment and the comfort of the E4 wristband was obtained from the study participants after the treatment session using a questionnaire (Appendix J,K) which was developed prior to the start of the study. The questionnaire also included some questions addressed to the parents/caregivers (Appendix L,M).

Chapter 3 Results

3.1. Sociodemographic characteristics

The initial sample consisted of 23 children, of which 11 were assigned to the control group and 12 to the study group. Of these, three (two from the control group and one from the study group) were excluded due to technical problems with the E4 wristband and one boy completed his treatment on the second appointment without IHS. As such, 20 children – 9 in the control and 11 in the study group– were included in the present analysis (Figure 5).

Figure 5 Study recruitment flow-chart



Participant sociodemographic characteristics are presented overall and by group in Table 2. The mean (SD) age of participants was 10.35 (2.41) years and there was no statistically significant difference between the study and control group (10.55 and 10.11 respectively, p-value=0.7). The minimum age was six years and the maximum, 15 years (figure 6).

There were slightly more boys than girls in the sample (n=11 or 55%) (figure 7). There were slightly less boys in the study group than in the control group (n=5 or 54.5% vs n=6 or 55.6%). Due to small sample size, Fisher's exact test was performed to compare the gender disparity between study and control group, and the gender was shown to be balanced between the two groups.

Table 2 Sociodemographic characteristics of participating children.

Sociodemographics	**Overall sample (N=20)**	**Study group (N=11)**	**Control group (N=9)**	**p-value***
Age, *mean (SD)*	10.35 (2.412)	10.55 (2.464)	10.11 (2.472)	0.700
Gender (boys), *n (%)*	11 (55%)	5 (54.5%)	6 (55.6%)	0.550

**Independent samples t-test to examine whether there was any difference in age between groups.*

***Fisher's exact test for the comparison of gender between groups.*

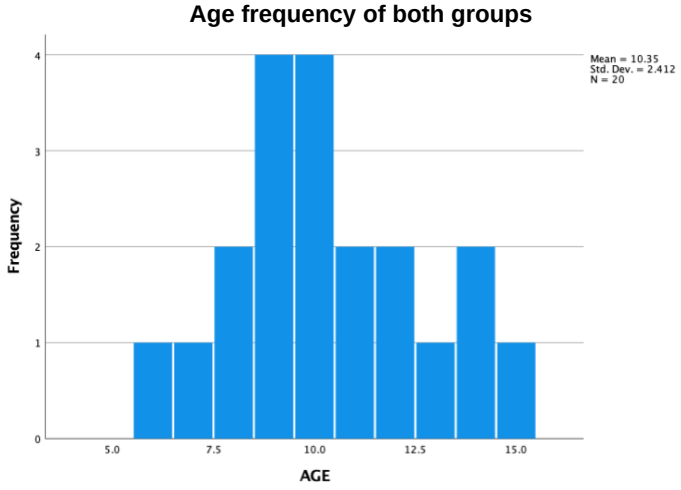


Figure 6 Frequency of age

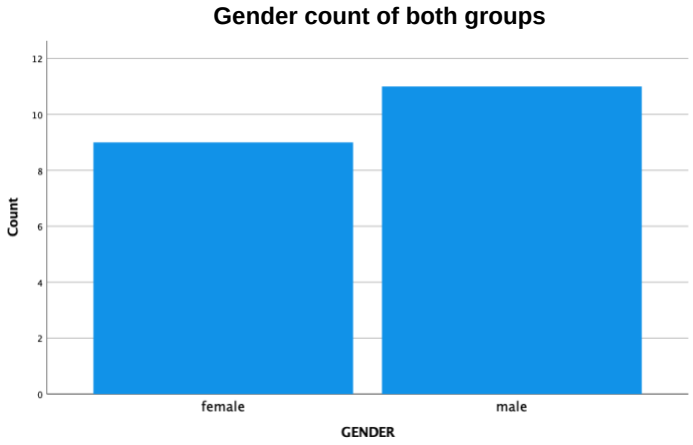


Figure 7 Gender count

3.2. Effect of experiencing N_2O/O_2 sedation vs not experiencing sedation at the assessment visit on children's dental anxiety

Dental anxiety was assessed using the $MCDAS_f$ questionnaire at three time points as follows:

- $MCDAS_f$ **1**: $MCDAS_f$ score at the beginning of the assessment visit (baseline)
- $MCDAS_f$ **2-1**: $MCDAS_f$ score at the beginning of the treatment visit (1^{st} follow-up)
- $MCDAS_f$ **2-2**: $MCDAS_f$ score at the end of the treatment visit (2^{nd} follow-up)

As shown in Table 3, the mean (SD) $MCDAS_f$ score was 21.55 (2.585) for the study group and 21.33 (2.398) for the control group at baseline and this reduced to 19.18 (7.922) and 14.11 (3.756) respectively at the end of the second visit. In general, children in the control group had the same mean $MCDAS_f$ scores as children in the study group during all assessments. There were no statistically significant differences in $MCDAS_f$ scores between groups at any assessment.

Table 3 Dental anxiety of children, as measured by the MCDAS$_f$ score, at each of the three assessments.

MCDAS$_f$,	**Overall sample (N=20),** *mean (SD)*	**Study group (N=11),** *mean (SD)*	**Control group (N=9),** *mean (SD)*	**p-value (T-test)***	**Study group, median (IQR)**	**Control group, median (IQR)**	**p-value (Mann-Whitney)****
MCDAS$_f$ **1**	21.55 (2.585)	21.73 (2.832)	21.33 (2.398)	0.744	22.00 (4)	21.00 (4)	0.701
MCDAS$_f$ **2-1**	19.55 (3.316)	20.36 (3.802)	18.56 (2.455)	0.235	20.00 (5)	18.00 (4)	0.319
MCDAS$_f$ **2-2**	16.90 (6.758)	19.18 (7.922)	14.11 (3.756)	0.096	19.00 (8)	15.00 (3)	0.134

**Independent samples t-test and **Mann-Whitney test to examine whether there was any difference MCDASf scores between groups during each assessment.*

Table 4 presents the changes in MCDAS$_f$ scores across assessments in each group, along with the comparisons of these changes between groups. There were statistically significant reductions in the changes in MCDAS$_f$ scores across measurements in the control group. However, none of the between-group differences in the changes of MCDAS$_f$ scores was statistically significant.

Table 4 Changes in $MCDAS_f$ scores across assessments in each group and the comparisons of these changes between groups.

	Study group (N=11)			Control group (N=9)			Between groups comparison		
$MCDAS_f$ change	**Mean (SD)**	**p-value* (T-test)**	**p-value* (Wilcoxon)**	**Mean (SD)**	**p-value* (T-test)**	**p-value* (Wilcoxon)**	**Mean (SE) Difference in change**	**p-value (T-test)****	**p-value (Mann-Whitney)*****
$MCDAS_f$ **1** – $MCDAS_f$ **2-1**	1.364 (3.075)	0.172	0.183	2.778 (2.489)	0.010	0.020	-1.414 (1.272)	0.281	0.280
MCDASf **2-1** – $MCDAS_f$ **2-2**	1.182 (7.181)	0.597	0.154	4.444 (4.216)	0.013	0.021	-3.263 (2.717)	0.245	0.285
$MCDAS_f$ **1** – $MCDAS_f$ **2-2**	2.546 (8.017)	0.317	0.074	7.222 (5.118)	0.003	0.013	-4.677 (3.093)	0.148	0.128

Paired t-tests (or Wilcoxon sign rank tests) **in each group to examine whether each score change was significant **between measurements***

***Independent samples' t-test (or Mann-Whitney test) to examine whether the difference in each score change **between groups** was significant.*

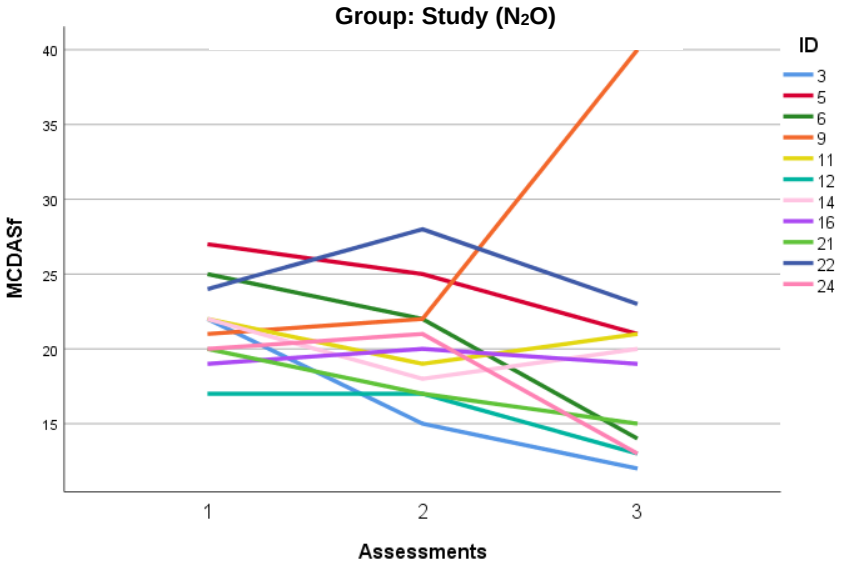


Figure 8 Change in MCDASf scores for each individual during the three assessment points in the study group

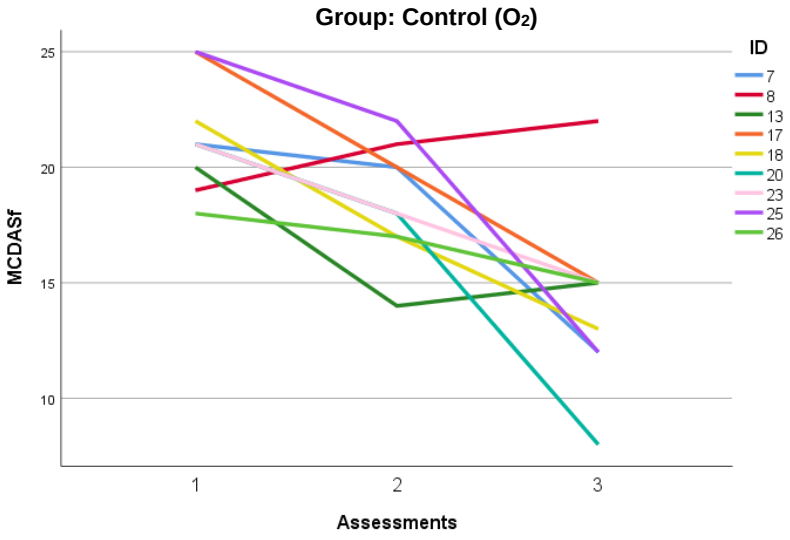


Figure 9 Change in MCDASf scores for each individual during the three assessment points in the control group

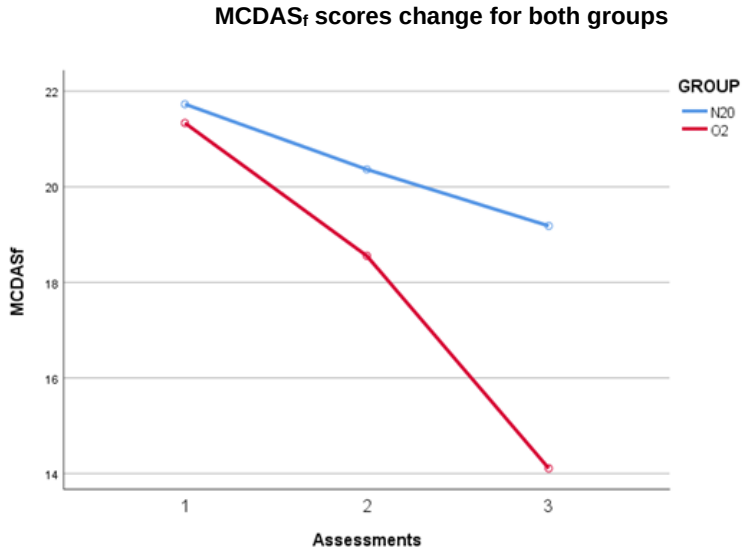


Figure 10 Overall change in MCDAS$_f$ scores between control and study groups over the three assessment points

3.3. Differences in children's dental anxiety levels before and after the treatment session

As shown in Table 4 above, the mean (SD) change in MCDAS$_f$ scores between the beginning and the end of the treatment visit for the study group was 1.182 (7.181). It was not statistically significant (paired t-test p-value=0.597 and Wilcoxon p-value=0.154). The respective mean (SD) change for the control group was 4.444 (4.216) and it was statistically significant (paired t-test p-value=0.0.13 and Wilcoxon p-value=0.021). The mean difference of this change between the study group versus the control group was -3.263 (2.717) and it was not statistically significant (t-test p-value=0.245 and Mann-Whitney p-value=0.285).

3.4. Children's acceptance of treatment

Treatment acceptance was examined using the Houpt anxiety score criteria at the assessment visit (Houpt 1) and at the treatment visit (Houpt 2). As shown in Table 5, the mean (SD) Houpt score was 6 (0) in both groups at the assessment visit. At the treatment visit the Houpt score reduced to 4.91 (1.3) in the study and 5.44 (1.13) in the control group but this difference between groups was not statistically significant (t-test and Mann-Whitney test p-value=0.345 and 0.242 respectively).

Table 5 Treatment acceptance, as assessed by the Houpt criteria, at the assessment and the treatment visit.

Houpt, *mean (SD)*	**Overall sample (N=20)**	**Study group (N=11)**	**Control group (N=9)**	**p-value (T-test)***	**p-value (Mann-Whitney)****
Houpt1	6.000 (0)	6.000 (0)	6.000 (0)	-	-
Houpt2	5.15 (1.226)	4.91 (1.300)	5.44 (1.130)	0.345	0.242

**Independent samples t-test and **Mann-Whitney test to examine whether there was any difference MCDASf scores between groups during each assessment. Tests could not be computed for Houpt 1 since standard deviations of both groups are 0.*

Table 6 presents the change in Houpt scores among the assessments in each group, along with the comparison of this change between groups. The Houpt score was statistically significantly reduced between the two assessments in the study group (paired t-test and Wilcoxon test p values= 0.019 and 0.026 respectively), in contrast to the control group where this change was not statistically significant (paired t-test and Wilcoxon test p values= 0.179 and 0.180 respectively). The difference in the change of Houpt scores was not statistically significantly different also between the two groups.

Table 6 Change in Houpt score across assessments in each group and the comparison of this change between groups.

	Study group (N=11)			**Control group (N=9)**			**Between groups comparison**		
Houpt change	**Mean (SD)**	**p-value* (T-test)**	**p-value* (Wilcoxon)**	**Mean (SD)**	**p-value* (T-test)**	**p-value* (Wilcoxon)**	**Mean (SE) Difference in change**	**p-value (T-test)****	**p-value (Mann-Whitney)****
Houpt1 – Houpt2	1.091 (1.300)	0.019	0.026	0.556 (1.130)	0.179	0.180	0.535 (0.552)	0.345	0.245

*Paired t-tests (or Wilcoxon sign rank tests) **in each group** to examine whether each score change was significant **between measurements***

***Independent samples' t-test to examine whether the difference in each score change **between groups** was significant.*

3.5. Completion of treatment in the two groups

As shown in Table 7 and Figure 11, only one participant did not complete the treatment process. This participant belonged to the study group and as was unable to manage the treatment. The difference in completion rates between groups was not statistically significant (p-value=1.000).

Table 7 Completion rates of treatment, overall and by study group.

		GROUP			
		Total	N2O	O2	p-value
COMPLETED	Yes	19	10	9	
	No	1	1	0	1.000
Total		20	11	9	

** Fisher's exact test for the comparison of completion rates between groups.*

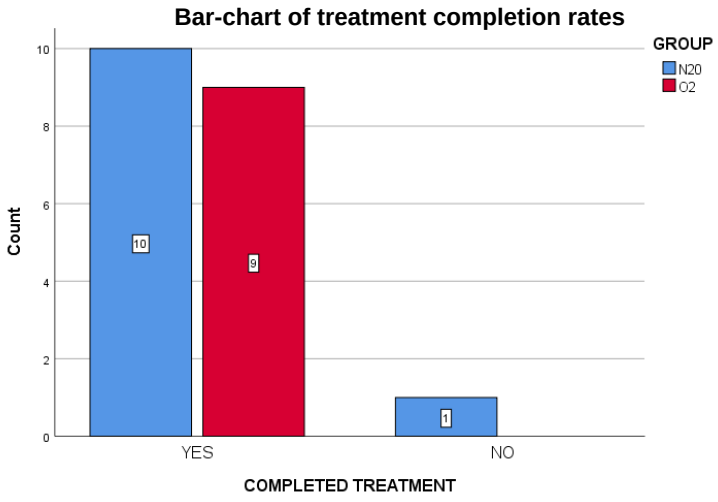


Figure 11 Clustered bar-chart of treatment completion rates by study group.

3.6. Children's physiological changes between the assessment to the treatment visit.

Physiological changes were assessed by recording children's Heart Rate (HR) and Skin Temperature (ST), as obtained by the E4 Wristband.

3.6.1 Heart rate:

HR was recorded during the assessment and the treatment visits. At each visit, three measurements were obtained for HR: 1) the baseline value, 2) the highest value and 3) the average HR value. We define:

- HR1: the difference between baseline and highest HR value during the assessment visit
- HR2: the difference between baseline and highest HR value during the treatment visit
- HR1 – HR2: the difference between HR1 and HR2
- Average HR1: average HR value during the assessment visit
- Average HR2: average HR value during the treatment visit

As shown in Table 8, HR1 was not statistically significantly different from HR2 in either group. Also, the differences in HR1 and HR2 were not statistically significantly different between groups (independent t-test and Mann-Whitney tests p-value = 0.628 and 0.970 respectively). The mean (SD) of average heart rate during the assessment visit was 76.661 (5.612) for the study group and 75.777 (8.311) for the control group and this between-groups' difference was not statistically significant (independent samples' t-test p-value=0.790 and Mann-Whitney test p-value=0.766). The mean of average heart rate during the treatment visit was 82.861 (7.469) for the study group and 77.105 (8.559) for the control group and this between-groups' difference was not statistically significant (independent samples' t-test p-value=0.133 and Mann-Whitney test p-value=0.201).

In the study group, the mean (SD) of the average heart rate was higher at the treatment visit [82.861 (7.469)] compared to the assessment visit [76.661 (5.612)] and this difference was of borderline statistical significance (paired-samples' t-test p-value=0.051 and Wilcoxon test p-value=0.050). The difference that was observed among assessments in the mean (SD) of the

average heart rate among participants of the control group was not statistically significant (paired-samples' t-test p-value=0.659 and Wilcoxon test p-value=0.859).Additionally, there was no statistically significant difference between groups in terms of the change that was observed in average HR from the assessment to the treatment visit (independent t-test and Mann-Whitney tests p-value = 0.224 and 0.184 respectively).

Table 8 Comparisons of heart rate (HR) related values across visits in each group and between groups.

	Study group (N=11)			Control group (N=9)			Between groups comparison		
	Mean (SD)	**p-value* (T-test)**	**p-value* (Wilcoxon)**	**Mean (SD)**	**p-value* (T-test)**	**p-value* (Wilcoxon)**	**Mean (SE) Difference**	**p-value (T-test)****	**p-value (Mann-Whitney)****
HR1 – HR2	0.985 (20.66)	0.878	0.594	-5.013 (14.45)	0.328	0.441	4.029 (8.163)	0.628	0.970
Average HR1- Average HR2	-6.201 (9.255)	0.051	0.050	-1.323 (8.693)	0.659	0.859	-4.872 (4.049)	0.224	0.184

Paired t-tests (or Wilcoxon sign rank tests)* ***in each group* *to examine whether changes in each group was significant* ***between visits***

Independent samples' t-test to examine whether the difference in changes* ***between groups *was significant.*

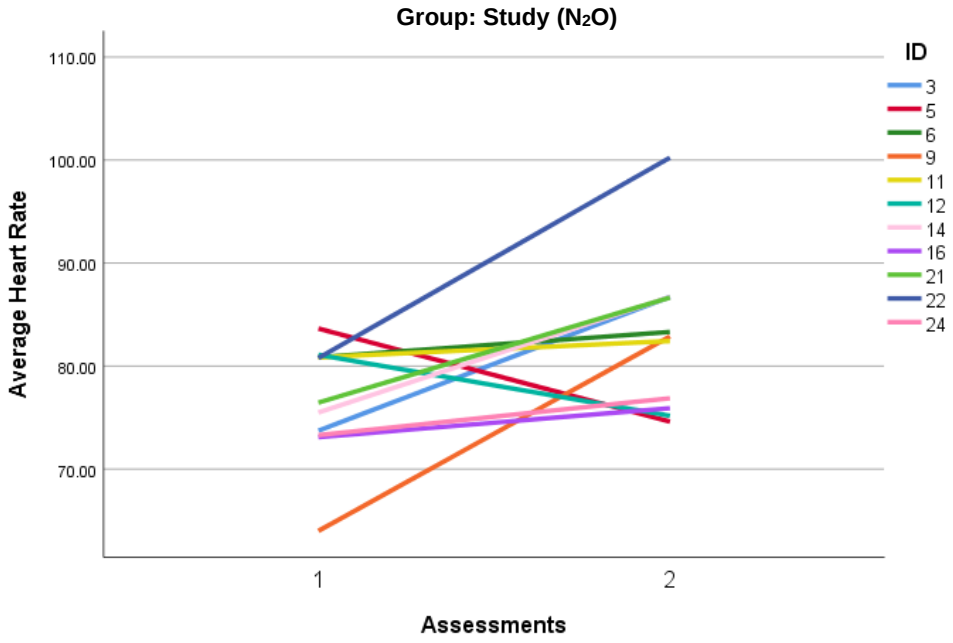


Figure 12 Change in average heart rate for each individual between the assessment (time 1) and the treatment visit (time 2) for the study group.

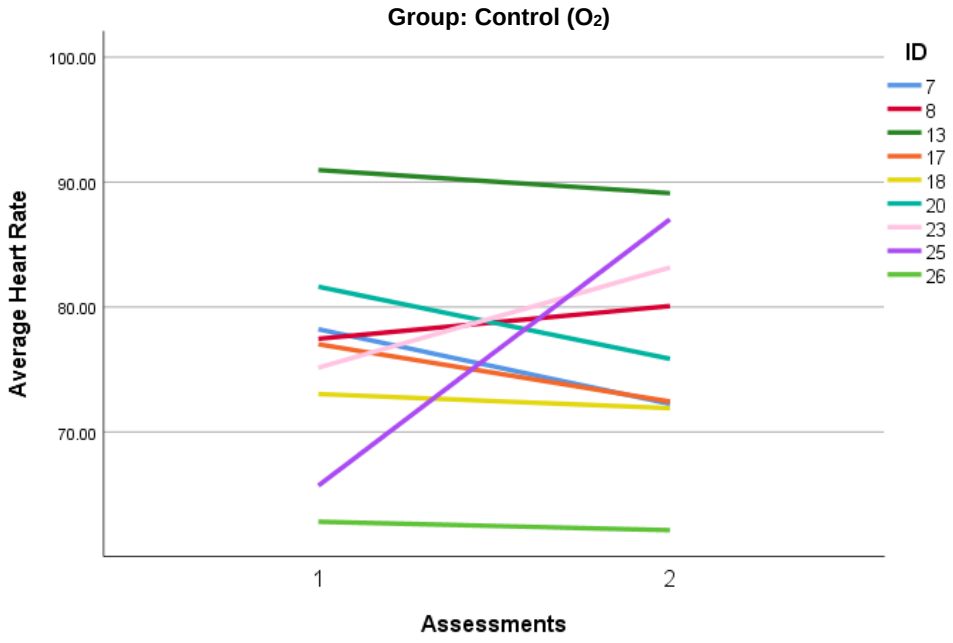


Figure 13 Change in average heart rate for each individual between the assessment (time 1) and the treatment visit (time 2) for the control group.

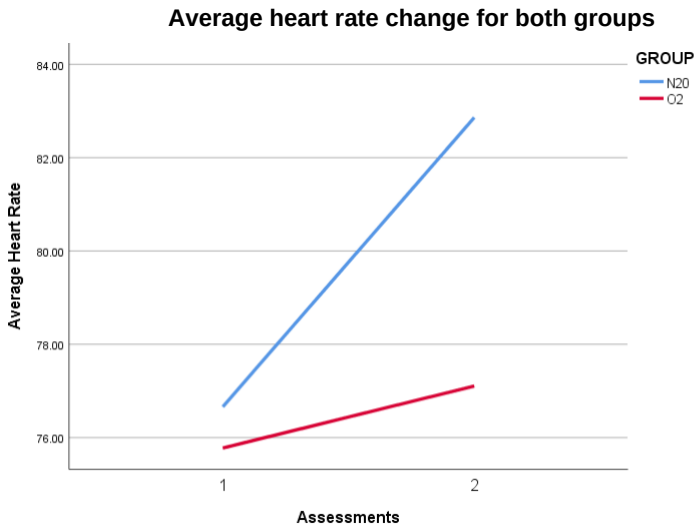


Figure 14 Overall change in heart rate between control and study group between the assessment (time 1) and the treatment visit (time 2)

3.6.2 Skin temperature:

The same analysis was conducted for skin temperature. We defined:

- ST1: the difference between baseline and highest ST value during the assessment visit
- ST2: the difference between baseline and highest ST value during the treatment visit
- ST1 – ST2: the difference between ST1 and ST2
- Average ST1: average ST value during the assessment visit
- Average ST2: average ST value during the treatment visit

As shown in Table 9, ST1 was not statistically significantly different from ST2 in either group. Also, the difference in ST1 and ST2 was not statistically significantly different between groups). Additionally, there was no statistically significant difference between groups in terms of the change in average ST. Finally, there were no statistically significant changes in either the ST1-ST2 or average ST across visits in either of the groups. The mean (SD) of the average ST1 was 33.326 (1.306) for the study group and 32.767 (1.451) for the control group. The mean (SD) of the average ST2 was 33.600 (1.673) for the study group and 33.059 (0.9395) for the control group.

Table 9 Comparisons of skin temperature (ST) related across visits in each group and between groups.

	Study group (N=11)			Control group (N=9)			Between groups comparison		
	Mean (SD)	**p-value* (T-test)**	**p-value* (Wilcoxon)**	**Mean (SD)**	**p-value* (T-test)**	**p-value* (Wilcoxon)**	**Mean (SE) Difference**	**p-value (T-test)****	**p-value (Mann-Whitney)****
ST1 – ST2	0.103 (1.350)	0.806	0.534	-0.143 (0.821)	0.614	0.484	0.246 (0.515)	0.638	0.382
Average ST1- Average ST2	-0.275 (2.016)	0.661	0.534	-0.292 (1.716)	0.624	0.767	-0.017 (0.843)	0.984	0.909

Paired t-tests (or Wilcoxon sign rank tests) **in each group to examine whether changes in each group was significant **between visits***

***Independent samples' t-test to examine whether the difference in changes **between groups** was significant.*

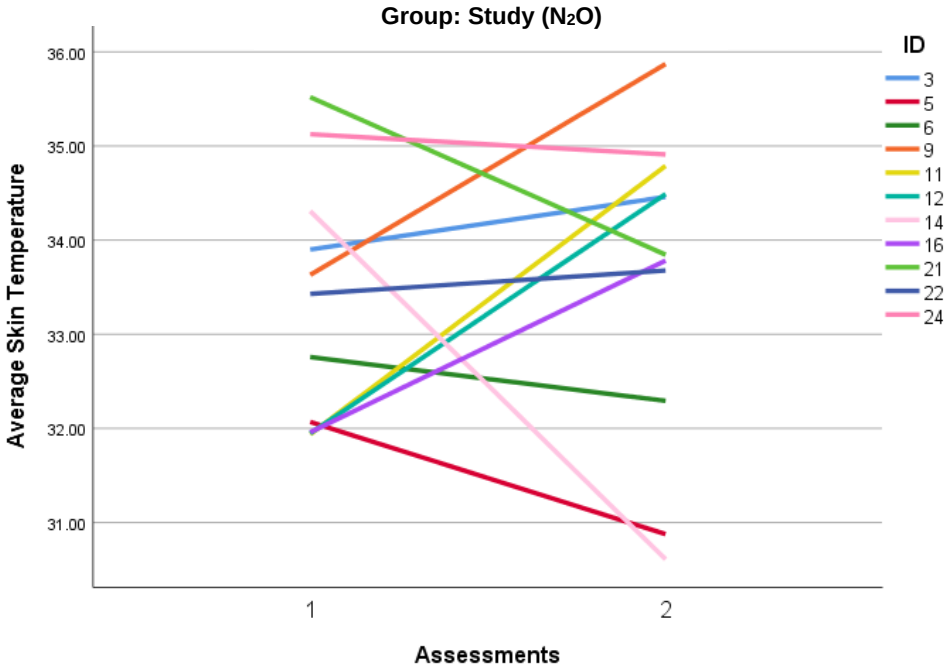


Figure 15 Change in average skin temperature [Celsius (°C)] for each individual between the assessment (time 1) and the treatment visit (time 2) for the study group

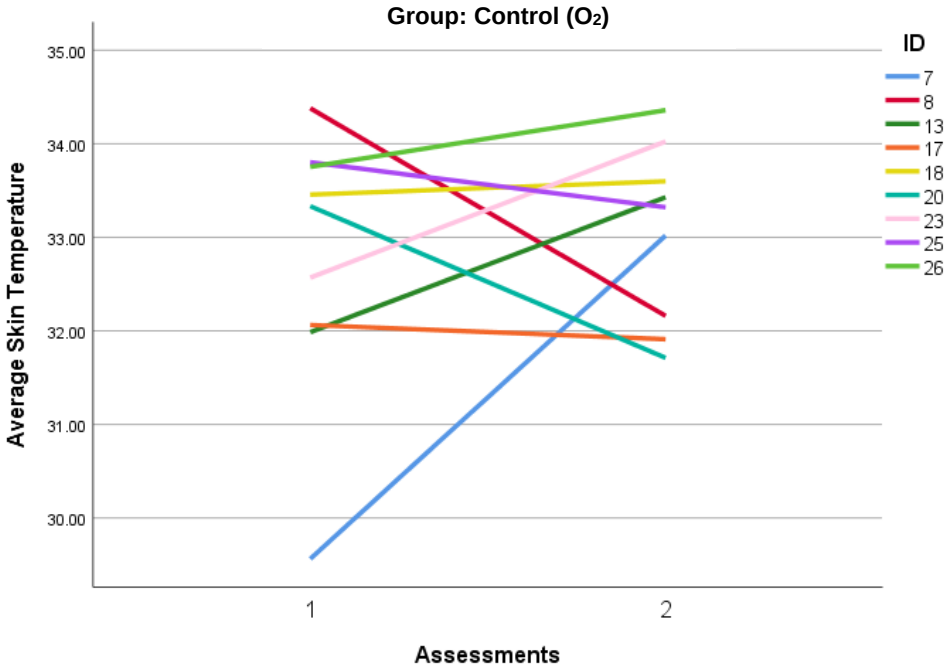


Figure 16 Change in average skin temperature [Celsius (°C)] for each individual between the assessment (time 1) and the treatment visit (time 2) for the control group

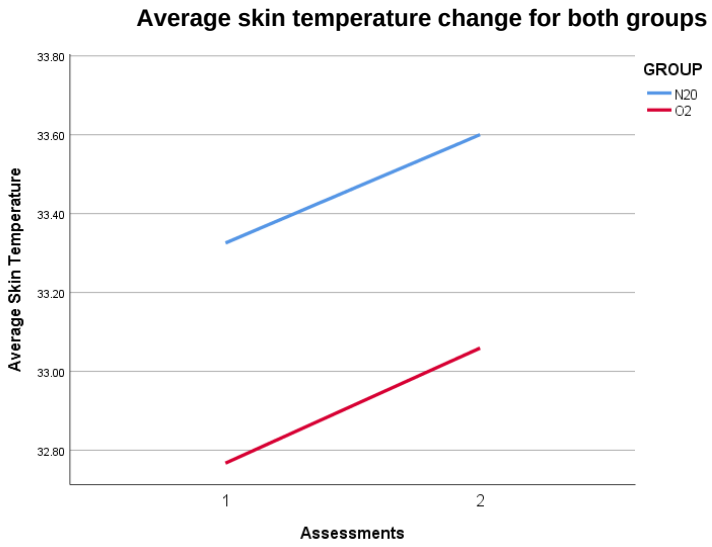


Figure 17 Overall change in average skin temperature [Celsius (°C)] between control and study group between the assessment (time 1) and the treatment visit (time 2)

3.7. Participant experience

Data on each participant's experience of the wristband are presented in Table 10. Only one child from each group found the wristband uncomfortable (n=2 or 15%) while more than half of them reported that it felt comfortable (n=13 or 65%) (Figure 18). Most participants in both groups agreed that trying the nose piece and N_2O/O_2 before the second visit would make them feel more relaxed (n=8 or 72.7% of the children in the study group and n=7 or 77.8% in the control group) (Figure 19 and Figure 20). No participant believed that it is not a good idea to try on the nose piece and N_2O/O_2 before the treatment visit.

Table 10 Children's experience

Patient's experience	**Overall sample (N=20)**	**Study group (N=11)**	**Control group (N=9)**
Wristband feeling, *N (%)*			
Uncomfortable	2(15)	1(11.1)	1(11.1)
Comfortable	13 (65)	7 (63.6)	6 (66.7)
No difference	5 (25)	3 (27.3)	2 (22.2)

Feeling on trying nose piece and magic gas before second visit, *N (%)*			
Less relaxed	1 (5)	1 (91)	0 (0)
More relaxed	15 (75)	8 (72.7)	7 (77.8)
No difference	4 (20)	2 (18.2)	2 (22.2)
Is it good idea to try on the nose piece and the magic gas on the first visit before treatment, *N (%).*			
Yes	16 (80)	8 (72.7)	8 (88.9)
No	0 (0)	0 (0)	0 (0)
Don't know	4 (20)	3 (27.3)	1 (11.1)

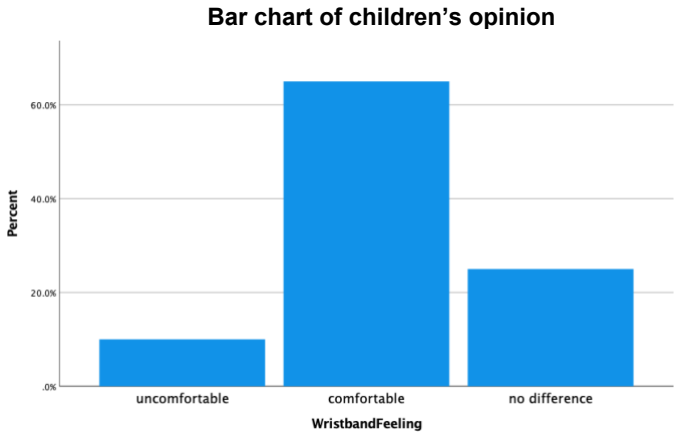


Figure 18 Children's opinion on how the wristband felt

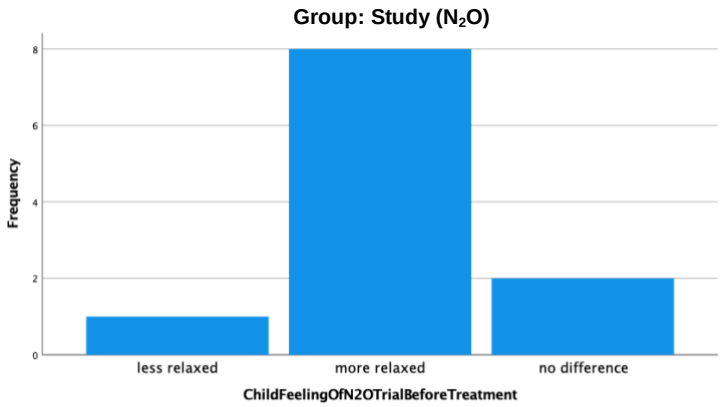


Figure 19 Children of the study group reported feeling

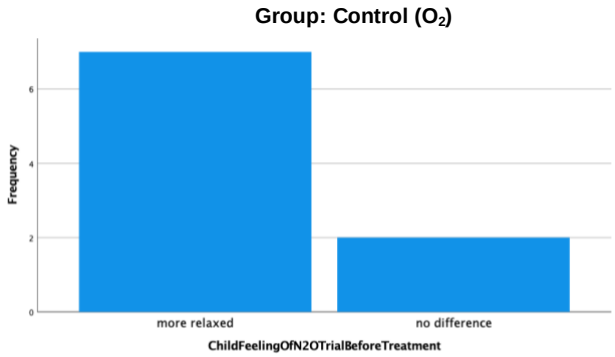


Figure 20 Children of the control group reported feeling

Data on the parents' experience of the visits are presented in Table 11. All but one of the parents of children in the study group agreed that children trying the nose piece and N_2O/O_2 before the second visit would make them feel more relaxed (n=10 or 90.9%) (Figure 21). The respective percentage of parents of children in the control group was 55.5% (n=5) (Figure 22), with a substantial proportion reporting that they thought it would make no difference (n=4 or 44.4%). All parents of children in the study group agreed that it would be a good idea to try the nose piece and N_2O on the first visit before treatment. The respective percentage of parents of children in the control group was 66.7% (n=6), with a substantial proportion reporting that they did not think it would be a good idea (n=2 or 22.2%).

Table 11 Parents' experience

Patient's experience	Overall sample (N=20)	Study group (N=11)	Control group (N=9)
How would trying nose piece and magic gas before treatment visit would make your child feel, *N (%)*			
Less relaxed	0 (0)	0 (0)	0 (0)
More relaxed	15 (75)	10 (90.9)	5 (55.6)
No difference	5 (25)	1 (9.1)	4 (44.4)
Is it good idea to try on the nose piece and the magic gas on the first visit before treatment, *N (%)*			
Yes	17 (85)	11 (100)	6 (66.7)
No	2 (10)	0 (0)	2 (22.2)
Don't know	1 (5)	0 (0)	1 (11.1)

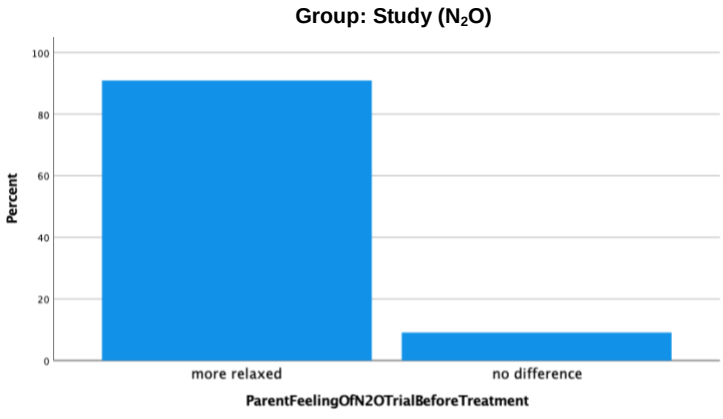


Figure 21 Parents of the study group report of their children's experience

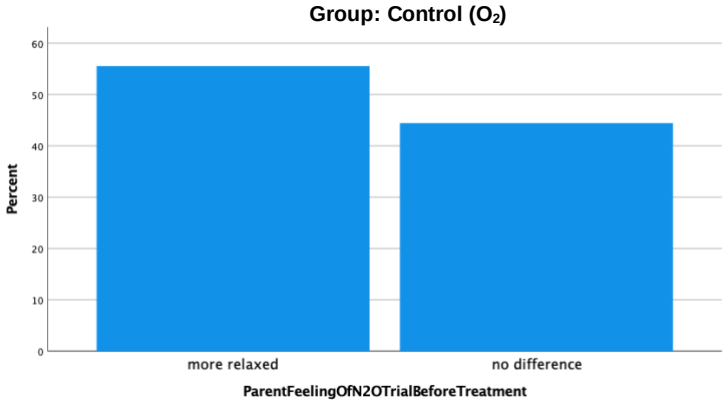


Figure 22 **Parents of the control group report of their children's experience**

Chapter 4 Discussion

4.1. Introduction

Dental anxiety is considered as an important problem affecting children's oral health and clinical management (Wu and Gao, 2018). Strategies to overcome dental anxiety are essential in order to improve children's oral health and their dental experience. This study aimed to assess the effect of experience of N_2O/O_2 sedation at assessment, prior to dental IHS on children's anxiety. Understanding is important especially in an environment of high waiting lists. If an acclimatisation visit does not prove effective, then it may be a waste of parent and hospital resources. The secondary aims of the study were to examine its effect on the completion and level of acceptance treatment and patient experience.

To the best of our knowledge there was no previous research specifically investigating the effect of acclimatisation on child anxiety and success of completion of treatment under inhalation sedation. The Royal Colleges of Surgeons and the Royal College of Anaesthetists in 2015 and SDCEP in 2017, recommended two visits for inhalation sedation, one preparatory one for the actual treatment. However, the recommendations are based on expert opinions and are not evidence based. Therefore, the study aimed to provide evidence to support the experts' opinion regarding the implementation of an acclimatisation visit.

A randomised non-blinded controlled clinical trial design was chosen which provides the highest level of evidence. The COVID-19 had a significant impact on the research leading to a significantly smaller sample size.

4.2. Covid 19

The COVID-19 pandemic has affected dentistry as every medical profession worldwide (Peng et al., 2020). The effect on dentistry is considerable, since most of the treatments involve aerosol-generating procedures which are more likely to spread the infection (Mallineni et al., 2020). During the first pandemic outbreak routine dental treatment was postponed and only severe

dental paediatric emergencies (such as discomfort, pain, swelling, life endangering dentigerous infection, traumatic dental injuries, etc.) were performed (Paglia, 2020).

LDI served only emergency dental procedures from March 2020 until November 2020. This meant that in spite of having received all approvals during the period from March to November 2020 no participants could be recruited for the study. Once the clinics started operation in November, to correctly carry out all the pre and postoperative sanitisation procedures and to avoid crowding of patients (and parents/caregivers) in the waiting room, the total number of patients treated daily was reduced (Cianetti et al., 2020). Therefore, it was impossible to achieve the initially expected sample size within the time frame of the research.

4.3. Study Design and Methodology

4.3.1 Sample size and sample selection

At the time of study design, there was a lack of published articles conducting similar research. Advice was sought from a qualified statistician at the University of Leeds and it was decided to follow the Lancaster et al., 2004 pilot study design. It was suggested to recruit a total of 68 participants (34 in each group) to ensure an appropriate and statistically valid sample size that would successfully answer the research hypotheses. However due to Covid-19 quarantine and new measures it was impossible to achieve our sample size and we only managed to recruit 23 participants in a period of 7 months.

The significantly reduced sample size is considered the greatest limitation of this study which affects the ability to generalise the results. The ideal study is the one which has high power to detect statistical significance. The power of the study depends on several factors, but as a general rule, higher power is achieved by increasing the sample size (Mohar and Dulbarg, 1994). Decreasing the sample size reduces the confidence level of the study and increases the margin of error. A study with a small sample size will have large confidence intervals and will only show up as statistically abnormal if there is a large difference between the two groups. In small sample sizes there is an increased probability of a type II error. This type of error takes

place when the null hypothesis is incorrectly accepted, and this causes a false-negative result.

The ability to generalise the results is further influenced by the population that the sample was drawn from. More specifically, it was a convenience sample drown by children that were referred to LDI. Children who are referred to the hospital usually require complex dental care and most of the time they are referred because they're too anxious to be treated by their regular general dental practitioner. Therefore, the are likely to have higher level of anxiety and disease compared to the normal which may affect the generalisability of the results as it’s a specific group.

4.3.2 Acclimatisation and treatment visit

Dental prophylaxis was only performed during the first appointment for both groups, to be constant and make sure that the anxiety level was not affected by the treatment. Ideally the operator would be blinded to the previous experience of the child. However, this would require an additional operator to perform the second visit and we know that the behaviour of the operator and the dental team influences the dental anxiety level of the patient. An operator may instill a positive attitude and minimise chances for dental anxiety while a different one may exaggerate, dental anxiety in patients (Appukuttan et al., 2020). To remove the effect of the operator, the Lead Researcher was the responsible dentist for both the appointments and blinding was not possible. For the first visit, blinding was not performed for safety reasons. In a recent Cochrane review, Paul et al., (2018) acknowledged that in trials of sedative agents in children, blinding of dental operators is difficult due to the nature of the equipment and drugs involved, and the need to ensure patient safety during the procedure.

Every other parameter apart from the use of N_2O/O_2 IHS, on the assessment visit, was tried to be kept as similar as possible for both groups to be able to focus on the effect of N_2O/O_2 sedation only. The IHS mask and equipment were explained and demonstrated and both groups tried on the mask. It is likely that just the act of putting the mask on and providing preparatory information may had a beneficial effect on the anxiety. It is known that by introducing children with some information about the upcoming dental

treatment may facilitate it (Newton et al., 2012). The sequence of the events at the treatment visit was kept the same for both groups.

The type of treatment carried out on the treatment session was not controlled i.e., participants were treated as per their treatment plan. We did not feel that it was an important factor to control as the primary outcome involved the assessment visit. Nevertheless, data obtained from this study demonstrated that dental extraction was the most common procedure received in both groups.

4.4. Anxiety scale

As a subjective parameter, anxiety was recorded with the help of the $MCDAS_f$ questionnaire in both groups. Research has indicated that children are able to self-report their anxieties by questionnaires from the age of five (Humphris et al., 2002). The $MCDAS_f$ was chosen as it is more versatile to be used for measuring dental anxiety over a wider age range for children (from three years old) and those with limited cognitive functioning (Christophorou et al., 2000; Howard and Freeman 2007; Porritt et al., 2013). The $MCDAS_f$ is reliable, short, and fast measure for child dental anxiety assessment (Javadinejad et al., 2011) and has been validated in di different populations and cultures (Leko et al., 2020). Furthermore, the $MCDAS_f$ questionnaire is routinely used at the SU at LDI and it is a useful tool in quantifying the degree of anxiety that children have.

The Lead Researcher was present during the completion of the questionnaires but did not influence any of the responses. For younger children, the questions were read out and the children pointed to the appropriate face on the scale which best described their anxiety level. Older children aged over 8 years were able to complete the questionnaire without assistance.

4.5. E4 wristband to measure physiological signals

Several studies have found increased anxiety causes physiological changes including increased respirations and heart rate and decreased peripheral

skin temperature (Prato, 2009). Heart rate and skin temperature were chosen for analysis, because they are simple biological parameters to measure. An increase in the heart rate is the most common physiologic indicator for anxiety (Erten et al., 2006). Studies by Jimeno et al. (2011) have shown that HR is a reliable and safe indicator of anxiety. The normal heart rate was considered around 90-95 beats per minute based on Fleming et al. (2011) results of a systematic review of 59 studies. Children aged six and seven were found to have a median heart rate of 90-95 beats per minute.

The physiological signals were measured through the wearable device Empatica E4 wristband (Empatica, Milan, Italy) which measurements have demonstrated high quality and validity (McCarthy et al., 2016; Ollander et al., 2016; Schuurmans et al., 2020; Milstein and Gordon 2020). The Lead Researcher placed the E4 wristband around the wrist of the non-dominant hand of each participant, at every appointment.

4.6. Feedback Questionnaire

Two simple questionnaires containing easy questions were designed by the Lead investigator for children and their carers. Prior to the start of the current study, the questionnaire was piloted in children aged 5-15 years old to evaluate its ease of understanding. The questionnaire was piloted in the Sedation Unit at Leeds Dental Institute, where ten children who were coming for their routine dental visits and their parents, were asked to complete the questionnaire and to provide comments. Feedback and comments were collected, and the majority of the children found it clear and easy to read and understand. The questionnaire took around 2-5 minutes to complete. Minor amendments were made following this pilot test, this included simplifying one question and adding smiley face Likert scale to make it clearer and more understandable.

4.7. Discussion of the Results

4.7.1 Demographics

4.7.1.1 Age

The statistical analysis results failed to find any statistically significant difference between the mean ages of the participants in the study and control groups. This is important because even though there is conflicting evidence regarding the effect of age on dental anxiety, previous research suggests that age could impact upon dental anxiety (Schuller et al., 2003; Armfield et al., 2007).

4.7.1.2 Gender

Due to small sample size, Fisher's exact test was performed to compare the gender disparity between study and control group. The gender was balanced between the two groups. If there had been a significant difference in the genders between the two groups, this could have been a potential source of bias as some studies who examined dental anxiety among young adolescent patients concluded that girls were more anxious than boys (Peretz and Efrat, 2000).

4.7.2 Effect of experiencing N_2O/O_2 sedation at the assessment visit on children's dental anxiety

The primary outcome of this study was to examine the effect of trying the N_2O/O_2 IHS on the assessment visit. The mean (SD) $MCDAS_f$ score was 21.73 (2.832) for the study group and 21.33 (2.398) for the control group at baseline. Children with a score ≥19 are considered to have severe dental anxiety, while those with a score of <19 are considered to have none to moderate anxiety (McDonnell-Boudra et al., 2014). This means that our sample is very anxious which is reasonable as dental anxiety is one of the indications of IHS.

There was no statistically significant difference in the difference of the $MCDAS_f$ score from the first to the second visit between the two groups. Therefore our null hypothesis is not rejected. Due to the small sample we can only interpret the statistical results with caution.

We found a statistically significant reduction in the $MCDAS_f$ score of the control group only, from the assessment visit to the beginning of the treatment visit. Regarding the study group, the non-statistical decrease may be a result of underpowering or that the exposure of the children to an additional N_2O intervention and increased patient contact time indeed raised their anxiety.

Another explanation is that we might have chosen a more anxious group of children by chance even though there was no difference on the baseline anxiety between the two groups. For the control group, the reduction could be true and attributed to the fact that the children had a short of an acclimatisation just by meeting the dentist and trying on the mask with O_2, even though N_2O/O_2 IHS was not tried. Taking into consideration that there was only a decrease on the dental anxiety level of the control group only we can assume that using nitrous at that acclimatisation visit is actually not a good idea and pre-treatment visit is effective but better not to use nitrous oxide at this visit

In order to try to keep things consistent we chose for the control group to try the mask with oxygen only. This however might have introduced bias as the fact that trying on the mask may have influenced the anxiety level. Children might have not been familiarised with the N_2O/O_2 IHS but they got familiar with the mask and the sedation equipment.

4.7.3 Difference in children's dental anxiety levels before and after the treatment session

The $MCDAS_f$ score was reduced in both groups at the end of the treatment visit even though this difference did not reach statistical significance between the two groups. This reduction was only statistically significant for the control group. The results point to a tendency for an acclimatisation visit to work but that it makes no difference if N_2O/O_2 IHS is actually experienced at that visit.

Another factor that helped both groups was the possibility to practise breathing with the mask so that at the treatment visit this was already sorted out. That is a real benefit because if children can't breathe through their

noses then the treatment has to be abandoned and a longer treatment time is not wasted.

It is important to address that the dental treatment of the children in the present study was performed by a postgraduate paediatric dentist who is training in special skills and behaviour management techniques for children. This may be a reason for the decrease in the children's levels of dental anxiety. One could hypothesise that, in the hands of general practitioners, the outcomes could be different. The level of experience is an important factor to consider when use of inhalation sedation is being investigated, where the psychological reassurance ability of the dentist is important (Paterson and Tahmassebi, 2003).

4.7.4 Physiological measurements

The results of the physiological measurements did not point any statistically significant difference between the groups, only a minor increase in the average HR from the assessment to the treatment visit in the study group only. The results of the HR are not consistent with the $MCDAS_f$ results. In the study group the $MCDAS_f$ score was reduced even though it did not reach statistical significance, while the HR was increased. This can be attributed to the fact the $MCDAS_f$ measures the anxiety at one specific time whereas HR is averaged over a period of time. We can hypothise that the $MCDAS_f$ score was lower from the beginning of the assessment visit to the beginning of the treatment visit due to the acclimatisation and got even lower at the end of the treatment visit because they finished the procedure. In contrast the HR during the treatment visit was higher compared to the acclimatisation visit as it was measured throughout the procedure which was usually a dental extraction.

4.7.5 Acceptance of treatment:

The Houpt scale is routinely used in the sedation unit at Leeds dental institute for all patients and is recorded routinely in the patients' dental records. According to recent systematic reviews, section IV of the Houpt behavioural scare was used in the majority of the RCTs included in order to assess the behaviour in sedation (Ashley et al., 2018; Rossit et al., 2021). More specifically according to Ashley et al. (2018) over half of the studies

used the Houpt or a modified Houpt scoring system to record behaviour. The Houpt behavioural scale, assesses behaviour in an ordinal form (grade 1 to 6) where higher values equal better behaviour.

In the Soldani et al. (2009) study, there was no agreement between observers' Frankl scores given to child participants. Taking into consideration that scoring the behaviour of a child may vary across clinicians, the Lead researcher only performed the scoring on all the participants during both visits.

In our study during the first visit, prevention only was performed which is an easy and well accepted procedure. The Houpt score was the highest for all the participants in both groups. Following the treatment visit the behavioural score was significantly reduced in the study group only, even though the score difference between the two groups was not statistically significant. This is consistent with the HR physiological measurements, which were increased during the treatment visit for the study group. Overall, there is a trend in measurements. More specifically the dental anxiety scores indicated that there was a statistically significant reduction on the anxiety of the control group only, the results of the HR measurements indicate that the study group was more anxious during the second visit while the behavioural score of the study group was decreased significantly during the treatment visit.

Obviously, the treatment provided may well influence the behaviour and anxiety of the participant. However, the data obtained from this study demonstrated that dental extraction was the most common procedures received in both groups.

4.7.6 Completion of treatment:

Completion of dental treatment has been widely used as a success criterion for sedation procedures in dentistry (Shepherd and Hill 2000; Hennequin et al., 2004; Hennequin et al., 2012). The main advantage of this parameter is its objectivity and reproducibility (Takkar D., et al. 2015). Only one participant of the study group did not manage to complete the treatment due to lack of compliance. Even this slight difference is consistent with the rest of the findings where the control group outperformed the study group.

4.7.7 Feedback

Prior to discharge and following their recovery from sedation, the participants and their carers were provided with a questionnaire to give their feedback about the E4 wristband and N_2O/O_2 IHS trial. What is really interesting is that in contrast with the results, the parents and participants feedback is in favour of the N_2O/O_2 IHS trial on a separate visit before treatment. The majority of the participants (80%) pointed that it is a good idea to try the N_2O/O_2 sedation before the actual treatment while 75% and 72.9% of the control and study group respectively, felt that it made them or would make them feel more relaxed. The results of the parents/carers' feedback were in agreement with the participants. Since the results point that an acclimatisation visit alone with the use of the nitrous oxide had a positive effect on the anxiety it would be interesting if we had included an additional question on the feedback questionnaire. This additional question could ask if it's a good idea to have an extra visit before treatment for acclimatisation but without the trial of N_2O/O_2 IHS.

4.8. Limitations

It is preferred to be able to conduct a study that has adequate sample size and power so that the conclusions generated from the research can be confidently applied to the broader population. Therefore, the biggest limitation of this current study is the low sample size. In this light, our results have to be considered as pilot findings and need to be replicated in a larger sample.

As this research was completed in Leeds with children who were selected from the new patient clinic and referred for IHS sedation at LDI, the results are specific to this group of patients and this affects the ability to generalise the outcomes. A school sample is generally considered more representative.

The types of treatment which were carried out were not controlled. Therefore, the anxiety levels might have been influenced by the different treatment complexities, as literature indicates that invasive procedures such as extractions and are associated with higher reported anxiety (Maggirias and Locker 2002). The data obtained from this study may demonstrated that

dental extraction was the most common procedures received in both groups but it is an approximate statement which we cannot take fully into consideration as even the extraction complexity differs between the type of tooth (ie permanent vs primary).

Moreover, parents/carers who didn't speak English were excluded from this study. This may have limited the results, by excluding some potential participants and did not allow the impact of a pre-treatment visit to be assessed in children who may have more limited understanding because of language difficulties. Another limitation of the present study is the fact that both parents/carers and Lead Researcher were present when children responded to both anxiety and feedback questionnaires, which may led to reduced privacy and the children's answering in line with parents' expectations and social expectations.

4.9. Future Research

This research was affected by a number of limitations as previously outlined. Further research is needed with a larger sample size. The recruitment of larger numbers of participants would allow subgroup analysis according to several factors that may have an impact on the anxiety levels. Past dental and medical experiences of the child, socioeconomic factors, general health and parental anxiety are known to influence both dental anxiety and behaviour (Klingberg and Broberg, 2007; Alshoraim et al., 2018). The results will enable clinicians to spot the children that may benefit from an acclimatisation visit.

What we understand from this research is that having an acclimatisation visit seems to help while the role of experiencing N_2O/O_2 vs O2 alone is not as clear. There is currently a research protocol published which also plans to investigate the acclimatisation to N_2O/O_2, and this may provide some additional evidence on the effectiveness of experiencing N_2O/O_2 IHS before treatment (Kowash et., 2020). It would be interesting to compare an acclimatisation visit (even without a trial of the mask and breathing the gases) versus not having an acclimatisation visit at all and moving straight to treatment under sedation on the first visit. Furthermore, future research

including a more detailed questionnaire or qualitative interviews would be useful in order to explore the views of children and parents themselves. For instance, there might be “dental” benefit of an acclimatisation visit but there may be parental issues around travel, time of work.

Chapter 5 Conclusion

From the present study the following conclusions were made:

1. There was no significant difference in the level of dental anxiety between the children that experience N_2O/O_2 sedation at the assessment visit with those children that experience the mask with O_2 only. Therefore, the null hypothesis, was accepted.
2. There was no significant correlation between the N_2O/O_2 IHS experience on the assessment visit and the rate of acceptance and completion of treatment.
3. The group of children that did not experience the N_2O/O_2 IHS on the assessment visit had minor statistically significant reduction of the dental anxiety score from the assessment to the treatment visit. On the contrary, participants who experienced the N_2O/O_2 IHS appeared a lower behavioural score and an increased HR.
4. 80% of the participants expressed the view that it is a good idea to try the N_2O/O_2 sedation before the actual treatment.
5. Further research is required with a larger sample size to further clarify the study results in more detail.

List of References

Alshoraim, M.A., El-Housseiny, A.A., Farsi, N.M., Felemban, O.M, Alamoudi, N.M, Alandejani, A.A. 2018. Effects of child characteristics and dental history on dental fear: cross-sectional study. *BMC Oral Health*. 18, pp. 33.

American Psychiatric Association. 2013. Diagnostic and statistical manual of mental disorders. 5 ed. Washington: American Psychiatric Association.

Ashley, P.F, Chaudhary, M., Lourenço-Matharu, L. 2018. Sedation of children undergoing dental treatment. Cochrane Database Syst Rev.

Appukuttan, D.P., Cholan, P.K., Tadepalli, A., Subramanian, S. 2017. Evaluation of dental anxiety and its influence on dental visiting pattern among young adults in India: A multicenter cross sectional study. *Ann. Med. Res*. 7 (6), pp. 393-400.

Arnrup, K., Berggren, U., Broberg, A.G., Lundin, S.A., Hakeberg, M. 2002. Attitudes to dental care among parents of uncooperative vs. cooperative child dental patients. *Eur J Oral Sci.* 110, pp. 75-82.

Armfield, J.M., Stewart, J.F., Spencer, A.J. 2007. The vicious cycle of dental fear: exploring the interplay between oral health, service utilization and dental fear*. BMC Oral Health*. 7, pp. 1.

Armfield, J.M., Heaton, L.J. 2013. Management of fear and anxiety in dental clinic: a review. *Aust Dent J*. 58, pp. 390-407.

Armfield, J.M. 2010. Towards a better understanding of dental anxiety and fear: cognitions vs. experiences. *Eur J Oral Sci.* 118, pp. 259-64.

Armfield, J.M. 2010. How do we measure dental fear and what are we measuring anyway? *Oral Health Prev Dent*. 8, pp. 107-15.

Armfield, J.M, Spencer, A.J., & Stewart, J.F. 2006. Dental fear in Australia: who's afraid of the dentist? *Aust Dent J*. 51, pp. 78-85.

Becker, D.E., Rosenberg, M. 2008. Nitrous Oxide and the Inhalation Anesthetics. *Anesthesia Progress*. 55, pp. 124-131.

Bedi, R., Sutcliffe, P., Donnan, P., Barrett, N., McConnachie, J. 1992. Dental caries experience and prevalence of children afraid of dental treatment. *Commun Dent Oral Epidemiol*. 20 (6), pp. 368-71.

Benjamins, C. 1995. Psychophysiological measurement of dental anxiety. Thesis. Amsterdam: Academic Centre for Dentistry.

Berggren, U., Meynert, G. 1984. Dental fear and avoidance: causes, symptoms, and consequences. *J Am Dent Assoc*. 109, pp. 247−251.

British Dental Association advice. 2011. Conscious sedation. BDA.

Buchanan, H, Niven, N. 2002. Validation of Facial Image Scale to Assess Child Dental Anxiety. *Int J Paediatr Dent*. 12, pp. 47-52.

Buchanan, H. 2010. Assessing dental anxiety in children the Revised Smiley Faces Program. *Child Care Hlth Dev*. 36, pp. 534-538.

Cabibihan, J.J., Chauhan, S. 2016. Physiological responses to affective tele-touch during induced emotional stimuli. *IEEE Trans Affect Comput*. 8 (1), pp. 1-1.

Cabibihan, J.J., Javed, H., Aldosari, M., Frazier, T.W., Elbashir, H. 2016. Sensing Technologies for Autism Spectrum Disorder Screening and Intervention. *Sensors.* 17 (1), pp. 46.

Chapman, W.P., Arrowood, J.G., Beecher, H.K. 1943. The analgesic effects of nitrous oxide compared in man with morphine sulphate. *J Clin Invest*. 22, pp. 871.

Chapman, H.R., Kirby-Turner, N.C. 1999. Dental fear in children - a proposed model. *Br Dent J*. 187, pp. 408-412.

Christophorou, S., Lee, G.T.R., Humphris, G.M. 2000. The reliability and validity of the modified child dental anxiety scale: a study of Greek Cypriot school children. *Eur J Paediatr Dent*. 1 (2), pp. 75–81.

Cianetti, S., Pagano, S., Nardone, M., Lombardo, G. 2020. Model for Taking Care of Patients with Early Childhood Caries during the SARS-Cov-2 Pandemic. *Int J Environ Res Public Health*. 17, pp. 3751.

Clark, M., Brunick, A. 2003. Handbook of Nitrous Oxide and Oxygen Sedation. 2nd ed. St. Louis: Elsevier Mosby.

Cohen, L.A., Synder, T.L., La Belle, A.D. 1982. Correlates of dental anxiety in a university population. *J Pub H Dent.* 42 (3), pp. 228-35.

Corah, N.L. 1969. Development of a dental anxiety scale. *J Dent Res*. 48, pp. 596-596.

Coulthard, P., Bridgman, C.M., Gough, L., Longman, L., Pretty, I.A, Jenner, T. 2011. Estimating the need for dental sedation. 1. The Indicator of Sedation Need (IOSN) - a novel assessment tool. *Br Dent J*. 211 (5), pp. E10.

Critchley, H.D. 2002. Electrodermal responses: What happens in the brain. *Neuroscientist.* 8, pp. 132-142.

Dawson, M., Schell, A., Filion, D. 2000. The electrodermal system. In: Cacioppo J, Tassinary LG, Berntson GG, editors, Handbook of psychophysiology, Cam-bridge University Press, pp. 200–223.

De-Jongh, A., Muris, P., Hors, G.T., Duyx, M. 1995. Acquisition and maintenance of dental anxiety: the role of aversive experiences and cognitive factors. *Behav Res Ther*. 33, pp. 205-210.

De-Jongh, A. Fransen, J. Oosterink-Wubbe F., Aartman, I. 2006. Psychological trauma exposure and trauma symptoms among individuals with high and low levels of dental anxiety. *Eur J Oral Sci*. 114, pp. 286-292.

Donaldson, D., Meechan, J.G. 1995. The hazards of chronic exposure to nitrous oxide: An update. *Br Dent J*. 178 (3), pp. 95-100.

Dufresne, A., Prom Tep, S., Senechal, S., Courtemanche, F. 2010. Physiological Measures, Eye Tracking and Task Analysis to Track User Reactions in User Generated Content. *Proceedings of Measuring Behavior 2010*. (August 24-27), pp. 218-22.

Eli, I., Uziel, N., Blumensohn, R., Baht, R. 2004. Modulation of dental anxiety: the role of past experiences, psychopathologic traits and individual attachment patterns. *Br Dent J.* 196 (11), pp. 689-694.

Emmanouil, D.E., Quock, R.M. 2007. Advances in understanding the actions of nitrous oxide. *Anesth Prog*. 54, pp. 9-18.

Empatica, Inc. Available at: https://store.empatica.com/products/e4-wristband?variant=39588207747. [Accessed October 2018].

Enkling, N., Marwinski, G., Johren, P. 2006. Dental anxiety in a representative sample of representative sample of residents of a large German city. *Clin Oral Investig*. 10, pp. 84-91.

Erten, H., Akarslan, Z.Z., Bodrumlu, E. 2006. Dental fear and anxiety levels of patients attending a dental clinic. *Quintessence Int*. 37, pp. 304-10.

Field, A.P., Argyris, N.G., Knowles, K.A. 2001. Who's afraid of the big bad wolf: a prospective paradigm to test Rachman's indirect pathways in children. *Behav Res Ther*. 39, pp. 1259-1276.

Fleming, S., Thompson, M., Stevens, R., Heneghan, C., Plüddemann, A., Maconochie, I., Mant, D. 2011. Normal ranges of heart rate and respiratory

rate in children from birth to 18 years of age: A systematic review of observational studies. *The Lancet*. 377 (9770), pp. 1011-1018.

Folayan, M.O., Idehen, E.E., Ojo, O.O. 2004. The modulating effect of culture on the expression of dental anxiety in children: a literature review. *Int J Paediatr Dent*. 14 (4), pp. 241-45.

Foster, R.L., Park, J.H. 2012. An integrative review of literature examining psychometric properties of instruments measuring anxiety or fear in hospitalized children. *Pain Manag Nurs*. 13, pp. 94-106.

Franchini, K.G., Cowley, A.W. 2011. Autonomic control of cardiac function. In: Robertson D, Biaggioni I, Burnstock G, Low P, Paton J, editors, Primer on the autonomic nervous system, Academic Press. 134–138.

Galeotti, A., Garret Bernardin, A., D'Anto V., Ferrazzano, G.F., Gentile, T., Viarani, V., Cassabgi, G., Cantile, T. 2016. Inhalation conscious sedation with nitrous oxide and oxygen as alternative to general anesthesia in precooperative, fearful, and disabled pediatric dental patients: A large survey on 688 working sessions. *Biomed Res Int*. pp. 7289310.

General Dental Council (GDC). Maintaining standards. 2001. Available at: http://www.gdc-uk.org/pdfs/ms_full_nov2001.pdf. [Accessed October 2003].

Garbarino, M., Lai, M., Bender, D., Picard, R.W, Tognetti, S. 2014. Empatica e3 - a wearable wireless multi-sensor device for real-time computerized biofeedback and data acquisition. *Proc. 4th Int. Conf. Wirel. Mob. Commun. Healthc.* pp. 39-42.

Girdler, N.M., Hill, C.M. 1998. Sedation in dentistry. 1st ed. London: Wright

Guinot, J.F., Yuste, B.S., Cuardos, F.N.C., Lorente, R.A., Mercade, B.M. 2011. Objective and subjective measures for assessing anxiety in paediatric dental patients. *Eur Journal Paediatr Dent.* 12, pp. 239.

Gustafsson, A., Arnrup, K., Broberg, A.G., Bodin, L., Berggren, U. 2010. Child dental fear as measured with the Dental Subscale of the Children's Fear Survey. Schedule: the impact of referral status and type of informant (child versus parent). *Community Dent Oral Epidemiol*. 38 (3), pp. 256-66.

Hägglin, C., Hakeberg, M., Ahlqwist, M., Sullivan, M., Berggren, U. 2000. Factors associated with dental anxiety and attendance in middle-aged and elderly women. *Community Dent Oral Epidemiol*. 28, pp. 451–60.

Hennequin, M., Collado, V., Faulks, D., Koscielny, S., Onody, P., Nicolas, E. 2012. A clinical trial of efficacy and safety of inhalation sedation with a 50%

nitrous oxide/oxygen premix (Kalinox™) in general practice. *Clin Oral Investig*. 16, pp. 633–642.

Hennequin, M., Manière, M.C., Albecker-Grappe, S., Faulks, D., Berthet, A., Tardieu, C., Droz, D., Wolikow, M., Koscielny, S., Onody, P. 2004. A prospective multicentric trial for effectiveness and tolerance of a N_2O/O_2 premix used as a sedative drug. *J Clin Psychopharmacol.* 24, pp. 552–554.

Hmud, R., Walsh, L. 2009. Dental anxiety: causes, complications, management approaches. *J Minim Interv Dent*. 2, pp. 67-78.

Hofmann, S.G. 2008. Cognitive processes during fear acquisition and extinction in animals and humans: implications for exposure therapy of anxiety disorders. *Clin Psychol Rev*. 28, pp. 199-210.

Holroyd, I. 2008. Conscious sedation in pediatric dentistry. A short review of the current UK guidelines and the technique of inhalational sedation with nitrous oxide. *Paediatr Anaesth*. 18 (1), pp. 13-17.

Holtzman, J.M., Berg, R.G., Mann, J., Berkey, D.B. 1997. The relationship of age and gender to fear and anxiety in response to dental care. *Spec Care Dentist*. 17, pp. 82-7.

Hosey, M. 2002. Managing anxious children: the use of conscious sedation in paediatric dentistry. *Int J Paediatr Dent*. 12, pp. 359-72.

Hosey, M., Blinkhorn, A.S. 1995. An evaluation of four methods of assessing the behaviour of anxious child dental patients. *Int J Paediatr Dent*. 5, pp. 87-95.

Houpt, M.I., Limb, R., Livingston, R.L. 2004. Clinical effects of nitrous oxide conscious sedation in children. *Pediatr Dent*. 24, pp. 289-294.

Howard, K., Freeman, R. 2007. Reliability and validity of a faces version of the Modified Child Dental Anxiety Scale. *Int J Paediatr Dent*. 17, pp. 281-288.

Humphris, G., Morrison, T., Lindsay, S. 1995. The Modified Dental Anxiety Scale: UK norms and evidence for validity. *Community Dent Hlth*. 12, pp. 143-150.

Humphris, G., King, K. 2001. The prevalence of dental anxiety across previous distressing experiences. *J Anxiety Disord.* 25, pp. 232-236.

Humphris, G., Milsom, K., Tickle, M., Holbrook, H., Blinkhorn, A. 2002. A new dental anxiety scale for 5-year-old children (DA5): description and concurrent validity. *Health Educ J*. 61 (1), pp. 5-19.

Javadinejad, S., Farajzadegan, Z., Madahain, M. 2011. Iranian version of a face version of the modified child dental anxiety scale: transcultural adaptation and reliability analysis. *J Res Med Sci*. 16 (7), pp. 872-7.

Jimeno, F.G., Bielsa, S.Y., Fernández, C.C., Rodríguez, A.L., Bellido, M.M. 2011. Objective and subjective measures for assessing anxiety in paediatric dental patients. *Eur J Paediatr Dent*. 12, pp.239-44.

Kemeny, M.E. 2003. The Psychobiology of Stress. Current Directions in Psychological Science. 12 (4), pp. 124-129.

Kleinhauz, M., Eli, I., Rubinstein, Z. 1985. Treatment of dental and dental related behavioral dysfunctions in a consultative outpatient clinic: A preliminary report. *Am J Clin Hypn*. 28, pp. 4-9.

Klingberg, G., Berggren, U., Carlsson, S.G., Noren J. G. 1995. Child dental fear: cause-related factors and clinical effects. *Eur J Oral Sci*. 103 (6), pp. 405-412.

Klingberg, G., Broberg, A.G. 2007. Dental fear/anxiety and dental behaviour management problems in children and adolescents: a review of prevalence and concomitant psychological factors. *Int J Paediatr Dent*. 17, pp. 391-406.

Klinberg, G. 2008. Dental anxiety and behaviour management problems in paediatric dentistry - a review of background factors and diagnostics. *Eur Arch Paediatr Dent*. 9, pp. 11-15.

Kowash, M., Al-Halabi, M., Hussein, I., Abdo, M.M., Salami, A., Hassan, A., Sverrisdottir, Y., Tahmassebi, J.F. 2020. A single-centre investigator-blinded randomised parallel-group study protocol to investigate the influence of an acclimatisation appointment on children’s behaviour during N2O/O2 sedation as measured by psychological, behavioural and real-time physiological parameters. *BDJ Open*. 6, pp. 5

Kupietzky, A., Tal, E., Shapira, J., Ram, D. 2008. Fasting state and episodes of vomiting in children receiving nitrous oxide for dental treatment. *Pediatr Dent*. 30 (5), pp. 414-9.

Kyritsi, M.A., Dimou, G., Lygidakis, N.A. 2001. Parental attitudes and perceptions affecting children's dental behaviour in Greek population. A clinical study. *Eur Arch Paediatr Dent*. 10 (1), pp. 29-32.

Lancaster, G.A., Dodd, S.R., Williamson, P.R. 2004. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract*. 10 (2), pp. 307-312.

Leko, J., Škrinjarić, T., Goršeta, K. 2020. Reliability and Validity of Scales for Assessing Child Dental Fear and Anxiety. *Acta Stomatol Croat*. 54(1), pp. 22-31.

Locker, D., Liddell, A., Dempster, L., Shapiro D. 1999. Age of onset of dental anxiety. *J Dent Res*. 78, pp. 790-796.

Locker, D., Poulton, R., Thomson, W. M. 2001. Psychological disorders and dental anxiety in a young population. *Commun Dent Oral Epidemiol.* 29, pp. 456-463.

Lourenco-Matharu, L., Ashley, P.F., Furness, S. 2012. Sedation of children undergoing dental treatment. Cochrane Database Syst Rev. 3:CD003877.

Luoto, A., Lahti, S., Nevanpera, T., Tolvanen, M., Locker, D. 2009. Oral-health-related quality of life among children with and without dental fear. *Int J Paediatr Dent*. 19, pp. 115-120.

Lyratzopoulos, G., Blain, K.M. 2003. Inhalation sedation with nitrous oxide as an alternative to dental general anaesthesia for children. *J Public Health Med*. 25 (4), pp. 303–312.

Maggirias, J., Locker, D. 2002. Psychological factors and perceptions of pain associated with dental treatment. *Community Dent Oral Epidemiol*. 30, pp. 151-9.

Malamed, S.F. 2018. Inhalation sedation: Techniques of administration. In: Sedation: A Guide to Patient Management. 6th ed. St. Louis, Mo.: Mosby Elsevier; pp. 227-52.

Mallineni, S.K., Innes, N.P., Raggio, D.P., Araujo, M.P., Robertson, M.D., Jayaraman, J. 2020. Coronavirus disease (COVID-19): Characteristics in children and conside- rations for dentists providing their care. *Int J Paediatr Dent*. 30, pp. 245-50.

McCarthy, C., Pradhan, N., Redpath, C., Adler, A. Validation of the Empatica E4 Wristband. In Proceedings of the 2016 IEEE EMBS International Student Conference (ISC), Ottawa, ON, Canada, 29–31 May 2016; pp. 1-4.

McDonnell-Boudra, D., Martin, A. & Hussein, I. 2014. In vivo exposure therapy for the treatment of an adult needle phobic. Dent. Update 41. pp. 533–536.

McGrath, C., Bedi, R. 2004. The association between dental anxiety and oral health-related quality of life in Britain. *Community Dent Oral Epidemiol*. 32, pp. 67-72.

McNally, R.J, Steketee, G.S. 1985. The etiology and maintenance of severe animal phobias. *Behav Res Ther*. 23, pp. 431- 435.

Menzies, R.G., Clarke, J.C. 1995. The etiology of phobias: a non-associative account. *Clin Psychol Rev*. 15, pp. 23-48.

Milgrom, P., Fiset, L., Melnick, S., Weinstein, P. 1988. The prevalence and practice management consequences of dental fear in a major US city. *J Am Dent Assoc*. 116 (6), pp. 641-47.

Milstein, N., Gordon, I. 2020. Validating Measures of Electrodermal Activity and Heart Rate Variability Derived From the Empatica E4 Utilized in Research Settings That Involve Interactive Dyadic States. *Front. Behav. Neurosci.* 14, pp. 148.

Mohar, D., Dulbarg, C.S. 1994. Statistical power, sample size, and their reporting in randomized controlled trials. JAMA. 272, pp.122-4.

Morgan, P.H., Wright, L.E., Ingersoll, B.D., Seime, R.J. 1980. Children's perceptions of the dental experience. *J Dent Child.* 47 (4), pp. 243-45.

Moore, R., Birn, H., Kirkegaard, E., Brodsgaard, I., Scheutz. F. 1993. Prevalence and characteristics of dental anxiety in Danish adults. *Community Dent Oral Epidemiol.* 21, pp. 292-296.

Moore, R., Brodsgaard, I. 2001. Dentists' perceived stress and its relation to perceptions about anxious patients. *Community Dent Oral Epidemiol*. 29 (1), pp. 73-80.

Muris, P., Bodden, D., Merckelbach, H., Ollendick, T.H., King, N. 2003. Fear of the beast: a prospective study on the effects of negative information on childhood fear. *Behav Res Ther.* 41, pp. 195-208.

National Institute of Health and Care Excellence. 2010. Sedation under 19s: using sedation for diagnostic and therapeutic procedures. London: National Institute of Health and Care Excellence.

Newton,T., Asimakopoulou, K., Daly, B., Scambler, S., Scott, S. 2012.The management of dental anxiety: time for a sense of proportion? *Br. Dent. J*. 213 (6), pp. 271-274.

Newton, J. T., Buck, D. J. 2000. Anxiety and pain measures in dentistry: a guide to their quality and application. *J Am Dent Assoc.* 131, pp. 1449-57.

Noteboom, J.T., Barnholt, K.R., Enoka, R.M. 2001. Activation of the arousal response and impairment of performance increase with anxiety and stressor intensity. *J appl physiol*. 91 (5), pp. 2093–2101.

Nuttall, N. M., Gilbert, A., Morris, J. 2008. Children's dental anxiety in the United Kingdom in 2003. *J Dent*. 36, pp. 857-860.

Ollander, S., Godin, C., Campagne, A., Charbonnier, S. 2016. A comparison of wearable and stationary sensors for stress detection. In 2016 IEEE International Conference on Systems, Man, and Cybernetics. pp. 4362–4366.

Olumide, F., Newton, J.T., Dunne, S., Gilbert, D.B. 2009. Anticipatory anxiety in children visiting the dentist: lack of effect of preparatory information. *Int J Paediatr Dent*. 19, pp. 338-342.

Onorati, F., Regalia, G., Caborni, C., Migliorini, M., Bender, D., Poh, M.Z., Frazier, C., Kovitch Thropp, E., Mynatt, E.D., Bidwell, J., Mai, R., LaFrance W.C. Jr, Blum, A.S., Friedman, D., Loddenkemper, T., Mohammadpour-Touserkani, F., Reinsberger, C., Tognetti, S., Picard, R.W. 2017. Multicenter clinical assessment of improved wearable multimodal convulsive seizure detectors. *Epilepsia*. 58, pp. 1870-1879.

Oosterink, F., de Jongh, A., Aartman, I. 2008. The Level of Exposure-Dental Experiences Questionnaire (LOE-DEQ): a measure of severity of exposure to distressing dental events. *Eur J Oral Sci*. 116 (4), pp. 353-361.

Oosterink, F., de Jongh, A., Aartman, I. 2009. Negative events and their potential risk of precipitating pathological forms of dental anxiety. *J Anxiety Disord.* 23, pp. 451-457.

Ost, L.G., Hugdhal, K. 1985. Acquisition of blood and dental phobia and anxiety response patterns in clinical patients. *Behav Res Ther*. 23, pp. 27−34.

Paglia, L. 2020. COVID-19 and Paediatric Dentistry after the lockdown. *Eur J Paediatr Dent*. pp. 21:89.

Paryab, M., Hosseinbor, M. 2013. Dental anxiety and behavioral problems: A study of prevalence and related factors among a group of Iranian children aged 6-12. *J Indian Soc Pedod Prev Dent*. 31, pp. 82-6.

Paterson, S.A., Tahmassebi, J.E. 2003. Pediatric dentistry in the new millennium: Use of inhalation sedation in pediatric dentistry. *Dent Update*. 30 (7), pp. 350-6, 358.

Peng, X., Xu, X., Li, Y., Cheng, L., Zhou, X., Ren, B. 2020. Transmission routes of 2019-nCoV and controls in dental practice. *Int J Oral Sci*. 12, pp. 9.

Peretz, B., Efrat, J. 2000. Dental anxiety among young adolescent patients in Israel. *Int J Paediatr Dent*. 10, pp. 126-132.

Porritt, J. Buchanan, H., Hall, M., Gilchrist, F., Marshman Z. 2013. Assessing children's dental anxiety: a systematic review of current measures. *Community Dent Oral Epidemiol*, 41, pp. 130–142.

Poulton, R., Menzies, R.G. 2002. Non-associative fear acquisition: a review of the evidence from retrospective and longitudinal research. *Behav Res Ther*. 40, pp. 127-149.

Prato, C.A. 2009. Biofeedback assisted relaxation training program to decrease test anxiety in nursing students. UNLV Theses, Dissertations, Professional Papers, and Capstones.pp. 81.

Prins, P.J.M. 1994. Anxiety in medical settings. In T. H. Ollendick, N. J. King & W. Yule (Eds.), International Handbook of Phobic and Anxiety Disorders in Children and Adolescents. New York: Plenum Press.

Rafique, S., Banerjee, A., Fiske, J. 2008. Management of the petrified dental patient. *Dent Update.* 35 (3), pp. 196-8, 201-2.

Random integer generator. Available at: https://www.random.org/integers/?num=68&min=0&max=1&col=1&base=10&format=html&rnd=new

Rantavuori, K., Lahti, S., Hausen, H., Seppa, L., Karkkainen, S. 2004. Dental fear and oral health and family characteristics of Finnish children. *Acta Odontol Scand*, 62, pp. 207-13.

Rantavouri, K., Zerman, N., Ferro, R., Lahti, S. 2002. Relationship between children's first dental visit and their dental anxiety in the Veneto region of Italy. *Acta Odontol Scand*. 60, pp. 297-300.

Regalia, G., Onorati, F., Lai, M., Caborni, C., Picard, R.W. 2019. Multimodal wrist-worn devices for seizure detection and advancing research: Focus on the Empatica wristbands. *Epilepsy Res*. 153, pp. 79-82.

Rossit, M., Gil-Manich, V., Ribera-Uribe, J.M. 2021. Success rate of nitrous oxide-oxygen procedural sedation in dental patients: systematic review and meta-analysis. *J Dent Anesth Pain Med*. 21 (6), pp. 527-545.

Rudovic, O., Lee, J., Dai, M., Schuller, B., Picard, R.W. 2018. Personalized machine learning for robot perception of affect and engagement in autism therapy. *Sci Robot*. 3

Salem, K., Kousha, M., Anissian, A. 2012. Dental Fear and Concomitant Factors in 3-6 Year-old Children. *J Dent Res Dent Clin Dent Prospects*. 6 (2), pp. 70-4.

Schuurmans, AAT., de Looff, P., Nijhof, K.S., Rosada, C., Scholte, R.H.J., Popma, A., Otten, R. 2020. Validity of the Empatica E4 Wristband to Measure Heart Rate Variability (HRV) Parameters: a Comparison to Electrocardiography (ECG). *J Med Syst*. 44 (11), pp. 190.

Seligman, L.D., Hoveya, J.D., Chacona, K., Ollendick, T.H. 2017. Dental anxiety: An understudied problem in youth. *Clin Psychol Rev*. 55, pp. 25-40.

Shepherd, A.R., Hill, F.J. 2000. Orthodontic extractions: a comparative study of inhalation sedation and general anaesthesia. *Br Dent J*. 188, pp. 329-331.

Shinba, T., Kariya, N., Matsui, Y., Ozawa, N., Matsuda, Y., Yamamoto, K. 2008. Decrease in heart rate variability response to task is related to anxiety and depressiveness in normal subjects. *Psychiatry Clin Neurosci*. 62, pp. 603- 609.

Siirtola, P., Koskimäki, H., Mönttinen, H., Röning, J. 2018. Using Sleep Time Data from Wearable Sensors for Early Detection of Migraine Attacks. *Sensors*. 18 (5).

Schuller, A.A., Willumsen, T., Holst, D. 2013. Are there differences in oral health and oral health behaviour between individuals with high and low dental fear? *Community Dent Oral Epidemiol*. 31, pp. 116-21.

Sonnenberg, E., Venham, L. 1977. Human figure drawings as a measure of the child's response to dental visits. *ASDC J Dent Child*. 44 (6), pp. 438-42.

Spielberger, C.D. 1972. Conceptual and methodological issues in anxiety research. In CD Spielberger (Ed.), Anxiety: Current trends in theory and research (pp. 481-93). New York: Academic Press.

Stewart, R.D. 1985. Nitrous oxide sedation/analgesia in emergency medicine. *Ann Emerg Med.* 14, pp. 139-148.

Taani, M.Q. 2001. Dental fear among a young adult population. *Int Dent J*. 51 (2), pp. 62-6.

Taani, D.Q., El-Qaderi, S.S., Abu Alhaija, E.S. 2005. Dental anxiety in children and its relationship to dental caries and gingival condition. *Int J Dent Hyg*. 3, pp. 83-7.

Takkar, D., Rao, A., Shenoy, R., Rao, A., Saranya, B.S. 2015. Evaluation of nitrous oxide inhalation sedation during inferior alveolar block administration in children aged 7-10 years: a randomized control trial. *J Indian Soc Pedod Prev Dent*. 33, pp. 239–244.

Taj-Eldin, M., Ryan, C., O'Flynn, B., Galvin, P. 2018. A review of wearable solutions for physiological and emotional monitoring for use by people with Autism Spectrum Disorder and their caregivers. *Sensors*. 18 (12), pp. 4271

Themessl-Huber, M., Freeman, R., Humphris, G., MacGillivray, S., Terzi, N. 2010. Empirical evidence of the relationship between parental and child dental fear: a structured review and meta-analysis. *Int J Paediatr Dent.* 20, pp. 83-101.

Ten Berge, M., Veerkamp, J.S.J., Hoogstraten, J., Prins, P.J.M. 2002a. Childhood dental fear in the Netherlands: prevalence and normative data. *Community Dent Oral Epidemiol.* 30, pp. 101-107.

Tickle, M., Jones, C., Buchannan, K., Milsom, K.M., Blinkhorn, A.S., Humphris, G.M. 2009. A prospective study of dental anxiety in a cohort of children followed from 5 to 9 years of age. *Int J Pediatr Dent.* 19, pp. 225-32.

Townend, E., Dimigen, G., Fug D. 2000. A clinical study of child dental anxiety. *Behav Res Ther.* 38, pp. 31-36.

Vagg, P.R., Spielberger, C.D, O'Hearn Jr, T.P. 1980. Is the State-Trait Anxiety Inventory multidimensional? *Pers Individ Dif*. 1, pp. 207-14.

Versloot, J., Veerkamp, J., Hoogstraten, J. 2008. Dental anxiety and psychological functioning in children: its relationship with behaviour during treatment. *Eur Arch Paediatr Dent*, 9 (1), pp. 36-40.

Wardell, D. W., Engebretson, J. 2001. Biological correlates of Reiki touch healing. *Issues and Innovations in Nursing Practice*. 33, pp. 439-445.

Welbury, R., Duggal, M. and Hosey, M. 2018. Paediatric dentistry. 5th ed. Oxford: Oxford University Press.

Wogelius, P., Poulsen, S., Sorensen, H.T. 2003. Prevalence of dental anxiety and behavior management problems among six to eight years old Danish children. *Acta Odontol Scand*. 61 (3), pp. 178-83.

Wong, H., Humphris, G. 1998. Preliminary validation and reliability of the modified child dental anxiety scale. *Psychol rep.* 83, pp. 1179-1186.

Wu, L., Gao, X. 2018. Children's dental fear and anxiety: exploring family related factors. *BMC Oral Health*. 18 (1), pp. 1-10.

Standards for Conscious Sedation in the Provision of Dental Care. Report of the Intercollegiate Advisory Committee for Sedation in Dentistry 2015. The dental faculties of the royal colleges of surgeons and the Royal College of Anaesthetists

Scottish Dental Clinical Effectiveness Programme (SDCEP). 2017. Conscious Sedation in Dentistry Dental Clinical Guidance, 3rd edition. Dundee: Scottish Dental Clinical Effectiveness Programme

Taj-Eldin, M., Ryan, C., O'Flynn, B., Galvin, P. 2018. A Review of Wearable Solutions for Physiological and Emotional Monitoring for Use by People with Autism Spectrum Disorder and Their Caregivers. *Sensors.* 18 (12), pp. 4271.

Vieluf, S., Reinsberger, C., El Atrache, R. Jackson, M., Schubach, S., Ufongene, C., Loddenkemper, T., Meisel, C. 2020. Autonomic nervous system changes detected with peripheral sensors in the setting of epileptic seizures. *Sci Rep.* 10, pp. 11560.

Zhang, H.M., Xia, B., Wang, J.H., Xie, P., Huang, Q., Ge, L.H. 2013. Chinese version of a face version of the modified child dental anxiety scale: transcultural adaptation and evaluation. *Chinese J Stomatol.* 48 (7), pp. 403-8.

List of Abbreviations

AAPD	American Academy of Pediatric Dentistry
ANS	Autonomous Nervous System
ASA	American Society of Anaesthesiologists
BDA	British Dental Association
BII	Blood-Injection-Injury
CNS	Central Nervous System
CDAS	Corah`s Dental Anxiety Survey
CFSS	Children`s Fear Survey Schedule
CFSS-DS	Dental Subscale of the Children`s Fear Survey Schedule
CSV	Comma Separated Values
DSM	Diagnostic and Statistical Manual of Mental Disorders
EDA	Electrodermal Activity
FIS	Facial Image Scale
GABA	Gamma-Amino-Butyric Acid
GDC	General Dental Council
HR	Heart Rate
LDI	Leeds Dental Institute
IHS	Inhalation sedation
IV	Intravenous
MAC	Minimum Alveolar Concentration
MCDAS	Modified Child Dental Anxiety Scale
$MCDAS_f$	Faces version of the Modified Child Dental Anxiety Scale
MDAS	Modified Dental Anxiety Survey
N_2O	Nitrous Oxide
O_2	Oxygen
RCA	Royal College of Anaesthetists
RCT	Randomised Control Trial
SDCEP	Scottish Dental Clinical Effectiveness Programme

SFP	Smiley Faces Program
ST	Skin Temperature
SU	Sedation Unit
VPT	Venham picture test

Appendices

Appendix A Research Ethics Committee approval letter

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Miss Ioanna Palikaraki
Postgraduate student in Paediatric Dentistry
currently a full- time student doing a professional Doctorate Degree in Paediatric Dentistry at the University of Leeds
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16 July 2020

Dear Miss Palikaraki

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Effectiveness of experience of nitrous oxide/oxygen sedation at assessment on the dental anxiety of children progressing to treatment under inhalation sedation.**
IRAS project ID:	**270932**
Protocol number:	**N/A**
REC reference:	**20/NW/0157**
Sponsor	**University of Leeds**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **270932**. Please quote this on all correspondence.

Yours sincerely,
Amber Ecclestone

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Faculty NHS Research Ethics Officer*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
IRAS Application Form [IRAS_Form_27022020]		27 February 2020
Letter from funder		25 February 2020
Organisation Information Document		
Other [Patient journey]	1	08 April 2020
Other [Ethics comments]	3	08 April 2020
Participant consent form [Consent form]	3	08 April 2020
Participant consent form [Assent form]	4	08 April 2020
Participant information sheet (PIS) [parent information sheet]	5	08 April 2020
Participant information sheet (PIS) [children 11-15 years old information sheet]	4	08 April 2020
Participant information sheet (PIS) [children 05-10 years old information sheet]	5	08 April 2020
Research protocol or project proposal [Research protocol]	5	24 February 2020
Schedule of Events or SoECAT	2	25 February 2020
Summary CV for Chief Investigator (CI) [student's CV]		25 February 2020
Summary CV for student [Ioanna Palikaraki]		25 February 2020
Summary CV for supervisor (student research) [Jinous Tahmassebi]		25 February 2020
Summary CV for supervisor (student research) [Richard Balmer]		25 February 2020
Summary CV for supervisor (student research) [Jing Kang]		25 February 2020
Validated questionnaire [Questionnaire for parents of Group B]		
Validated questionnaire [Questionnaire for patients of Group B]		
Validated questionnaire [Questionnaire for patients of Group A]		
Validated questionnaire [Questionnaire for parents of Group A]		
Validated questionnaire [Anxiety questionnaire]		

IRAS project ID	270932

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is only one participating NHS organisation therefore there is only one site type.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	No study funding will be provided to sites as per the Organisation Information Document	A Principal Investigator should be appointed at study sites	No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain a Letter of Access based on enhanced DBS checks and occupational health clearance.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Appendix B Parent's Information sheet

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

Date:

IRAS project ID: 270932
V:5

School of Dentistry

Parent Information sheet

Research Title:

Effectiveness of experience of nitrous oxide/oxygen sedation at assessment on the dental anxiety of children progressing to treatment under inhalation sedation

Introduction:

My name is Ioanna Palikaraki and I am a Postgraduate student in the School of Dentistry at the University of Leeds. I would like to invite you and your child to take part in the above research study at Leeds Dental Institute.

Before you decide whether or not to take part, please take time to read the following information carefully in order to understand what this research is about and what your participation involves. Please feel free to discuss with other people and ask us if you wish to clarify any matters regarding this research. Taking part in the study will approximately add 5-10 minutes to your appointment.

Study Purpose

The purpose of this study is to find out the effect of experience of the nitrous oxide/oxygen sedation (relaxation gas) on children's behaviour before the actual treatment session. This study will be funded by the Faculty of Medicine and Health, University of Leeds.

Some Questions You May Have

Why have I been chosen?

You and your child have been chosen because your child is attending their first visit in the sedation unit at Leeds Dental Institute.

Who is eligible to participate?

We are inviting healthy children aged from 5 to 15 years attending the inhalation sedation unit who require dental care. They should not have had inhalation sedation treatment before and should be able to follow our instructions. We are excluding children who are not able to communicate directly with the dentist who is carrying out the treatment.

Do I have to take part?

You are not obliged to participate, **and this won't affect the treatment that your child is going to receive.** We will go through this information sheet and explain this study to you. At the first visit if you are willing to allow your child to participate in this study, we will ask you to sign a consent form and your child an assent form respectively, although you are free to withdraw from the study at any time without giving a reason.

What my child and I have to do?

We would like to ask your child some questions about how they feel at the moment (i.e. being at the dentist). Your child would be asked to answer these questions at the beginning of the first visit which will be an assessment visit and at the beginning and end of the second visit which will be a treatment visit. The questions will be asked through a simple questionnaire that will add about 10 minutes to the routine dental appointment. Additionally, your child will wear a wrist band similar to a watch throughout both appointments which measures the heart rate and skin temperature. During the first appointment, your child will be randomly assigned to one of two groups. One group will try on the nose piece and the relaxation gas during the first appointment before the treatment session while the other group will try on the nose piece without the relaxation gas. At the end of the treatment session we would like to ask each participant and his/her parent/legal guardian to provide some feedback through a short questionnaire.

Each participant will receive a battery charged toothbrush as a modest gift for their participation time.

What are the possible benefits of taking part?

We hope to understand more about the effect of experiencing the relaxation gas before the actual treatment session, which may help us improve the child's experience in the Sedation Unit.

What are the possible risks or disadvantages of taking part?

The possible risks or side effects are the same risks of having treatment under Inhalation sedation, which are very remote. There is a small possibility of getting nauseous or having a headache. Rarely, inhalation sedation may cause your child to vomit.

What will happen if I or my child decided not to continue with the study?

You can withdraw from the study at any time; this won't affect your child's treatment in any way. Unless you ask us not to, the information already collected shall be used in the analysis.

What will happen to the results of the research?

The information will be stored safely and securely in accordance with the Data Protection Act 2018. Any personal data collected shall be kept confidential and anonymised so that those reading reports from the research will not know who has contributed to it. The results of this study are intended to be used for Professional Doctorate research project by Ioanna Palikaraki and will be published in her thesis. **There will be no mention of specific individuals**.

The University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from your child medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Leeds will keep identifiable information about your child for 2 years after the study has finished until 2023.

Your rights to access, change or move your child's information are limited, as we need to manage your information in specific ways for the research to be reliable and accurate. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Leeds teaching Hospital NHS Trust will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Leeds and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Leeds teaching Hospital NHS Trust will pass these details to University of Leeds along with the information collected from you/or and your medical records. The only people in University of Leeds who will have access to information that identifies you will be people who need to contact you to the research or audit

the data collection process. The people who analyse the information will not be able to identify you and will not be able to find your name, NHS number or contact details. University of Leeds\LTHT will keep identifiable information about your child from this study for 2 years after the study has finished/ until 2023. You can find more about how we use your information by contacting the University of Leeds Data Protection Officer on DOP@leeds.ac.uk .

If you wish to find out more about how your data is used by UOL and generally in research, you can visit these webpages below:

https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/09/HRA-transparency-wording.pdf.
https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/02/Research-Privacy-Notice.pdf.

What if I need to complain?

You can contact the Faculty NHS Research Ethics Officer in the University of Leeds; their contact details are as follows:

Telephone: 01133437587

Email: governance-ethics@leeds.ac.uk

Office Address: Faculty Research Office-Room 9.29, Level 9, Worsley Building-Claredon Way Leeds-LS2 9NL

Who is organising and funding this research?

This research is funded by the Faculty of Medicine and Health, University of Leeds.

Who reviewed this study?

The University of Leeds has reviewed the study. This study has been granted ethical approval by the GM East NHS Research Ethics Committee.

Contact details for researchers:

- **Dr Richard Balmer**

  Consultant and Lecturer in Paediatric Dentistry
  School of Dentistry – University of Leeds
  Level 6 – Worsley Building – Clarendon Way – Leeds -LS2 9LU
  Email: r.c.balmer@leeds.ac.uk
  Telephone: 0113 3439218

- **Ms Ioanna Palikaraki**

Postgraduate in Paediatric Dentistry
School of Dentistry – University of Leeds
Level 6 – Worsley Building – Clarendon Way – Leeds -LS2 9LU
Email: dnip@leeds.ac.uk

Thank you for taking time to read this information sheet.

Appendix C Participant's Information Sheet (5-10 years old)

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

School of Dentistry

Date:

IRAS project ID: 270932
V:5

Child Information sheet (5-10 years)

A project to help dentists to make you feel more relaxed before they fix your teeth using the magic gas.

Who Am I?

My name is Ioanna Palikaraki and I am a dentist who treat children at Leeds Dental Institute.

What is the purpose of the study?

The aim of this study is to help dentists to make you feel more relaxed before they fix your teeth using the magic gas.

Why have I been chosen?

We chose you because you are here in the clinic today to have your teeth fixed.

What do I have to do?

You will need to answer some questions about how you feel at the moment (i.e. being at the dentist). You will also wear a special watch that will help us understand how fast your heart is working.

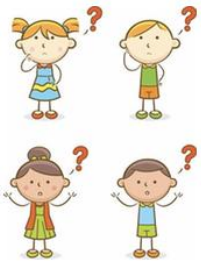
Do I have to take part?

No. It is up to you. You are free to stop taking part at any time during the research without giving a reason. If you decide to stop, this will not affect how we fix your teeth.

Will anyone now any information about you?

Your dentist and the research team only will know your information but will not share it with anyone else.

What if you have any questions?



If you have any other question you can send me an email or ask your parents or guardian to send me email on your behalf (dnip@leeds.ac.uk).

Thank you!

Appendix D Participant's Information Sheet (11-15 years old)

School of Dentistry
Date:

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS
IRAS project ID: 270932
V:4

Child Information sheet (11-15 years)

A project to help dentists to find out whether they can make you feel more relaxed before they fix your teeth using the magic gas.

Some Questions you may have

Who Am I?

My name is Ioanna Palikaraki and I am a dentist who treat children at Leeds Dental Institute.

What is the purpose of the study?

The purpose of the study is to help dentists to find out whether they can make you feel more relaxed before they fix your teeth using the magic gas.

Why have I been chosen?

We chose you because you are here in the clinic today to have your teeth fixed.

What do I have to do?

You will need to answer some questions about how you feel at the moment (i.e. being at the dentist). You will be asked to answer these questions at the beginning of your first visit and at the beginning and end of your second visit. The questions will be asked through a simple questionnaire that will add about 10 minutes to your routine dental appointment. You will also wear a special watch that will help us understand more about how you are feeling by measuring your heart rate and skin temperature.

Do I have to take part?

No. It is up to you. We will ask you for your permission and signature on our information forms. If you decide to take part, a copy of this information sheet with your signed form will be given to you. You are free to stop taking part at any time during the research without giving a reason. If you decide to stop, this will not affect how we fix your teeth.

What will happen if I decided not to continue with the study?

You can stop from the study at any time; this will not change your treatment in any way. Unless you have told us not to, we will use the information already collected.

Will anyone now any information about you?

Your dentist and the research team only will know your information but will not share it with anyone else.

What if you have any questions?

If you have further questions, you can contact Ms Ioanna Palikaraki or the lead supervisor, Dr Jinous Tahmassebi, through the following methods:

- **Dr Richard Balmer**

  Consultant and Lecturer in Paediatric Dentistry
  School of Dentistry – University of Leeds
  Level 6 – Worsley Building – Clarendon Way – Leeds -LS2 9LU
  Email: r.c.balmer@leeds.ac.uk
  Telephone: 0113 3439218

- **Ms Ioanna Palikaraki**

  Postgraduate in Paediatric Dentistry
  School of Dentistry – University of Leeds
  Level 6 – Worsley Building – Clarendon Way – Leeds -LS2 9LU
  Email: dnip@leeds.ac.uk

Thank you for taking time to read this information sheet.

Appendix E Consent form

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

School of Dentistry

IRAS project ID: 270932
V:2

Participant code: ☐

Project Title: Effectiveness of acclimatisation visit prior to Dental Nitrous Oxide Inhalation Sedation on children's anxiety.

Please initial the box if you agree with the statement to the left.

1	I confirm that I have read and understand the information sheet/letter explaining the above research project and I have had the opportunity to ask questions about the project.	☐
2	I understand that my participation and my child's are voluntary and that we are free to withdraw at any time without giving any reason and without there being any negative consequences. In addition, should we not wish to answer any particular question or questions, we are free to decline.	☐
3	I understand that my child's name will not be linked with the research materials, and we will not be identified or identifiable in the report or reports that result from the research.	☐
4	I agree my child's notes can be looked at by the researchers.	☐
5	I agree for the data collected from our participation can be used in future research and for educating dentist and the dental team.	☐
6	I and my child agree to take part in the above research project.	☐

_____ _____ _____

Name of participant Date Signature

(*or legal representative and relationship*)

Lead researcher	Date	Signature

To be signed and dated in presence of the participant

Copies:

Once this has been signed by all parties the participant should receive a copy of the signed and dated participant consent form, the letter/pre-written script/information sheet and any other written information provided to the participants. A copy of the signed and dated consent form should be kept with the project's main documents which must be kept in a secure location.

Appendix F Assent form

UNIVERSITY OF LEEDS

The Leeds Teaching Hospitals NHS
NHS Trust

School of Dentistry

IRAS project ID: 270932
V:3

Participant code: _____

Project Title:

A project to help dentists to make you feel more relaxed before they fix your teeth using the magic gas.

Please ***circle*** all that you agree with (if you are unable to do so, your parents may help you).

Have you read (or had read to you) about this project?	Yes/No
Has somebody else explained this project to you?	Yes/No
Do you understand what this project is about?	Yes/No
Have you asked all the questions you want?	Yes/No
Do you understand all the answers to your questions?	Yes/No
Do you understand it's OK to stop taking part at any time?	Yes/No
Are you happy to take part?	Yes/No

If <u>any</u> answers are 'No' or you do not want to take part, don't sign your name!

If you <u>do</u> want to take part, you can write your name on the next page

Name (Block Capitals): _____

Child's Signature: _____

Date: _____

The dentist who explained this project to you needs to sign too:

Name (Block Capitals): _____

Signature: _____

Date: _____

Appendix G Faces version of Modified Dental Anxiety Scale

IRAS project ID: 270932
V:1

Participant Code: [ ]

For the next eight questions I would like you to show me how relaxed or worried you get about the dentist and what happens at the dentist. To show me how relaxed or worried you feel, please use the simple scale below. The scale is like a ruler going from 1 which would show that you are relaxed, to 5 which would show that you are very worried.

1 would mean: *relaxed/not worried*
2 would mean: *very slightly worried*
3 would mean: *fairly worried*
2 would mean: *worried a lot*
3 would mean: *very worried*

Please circle the most applicable number to each of the following questions:

How do you feel about …					
… going to the dentist generally?	1	2	3	4	5
… having your teeth looked at?	1	2	3	4	5
… having your teeth scraped and polished?	1	2	3	4	5
… having an injection in the gum?	1	2	3	4	5
… having a filling?	1	2	3	4	5
… having a tooth taken out?	1	2	3	4	5
… being put to sleep to have treatment?	1	2	3	4	5
… having a mixture of 'gas and air' which will help you feel comfortable for treatment but cannot put you to sleep?	1	2	3	4	5

Thank you

Appendix H Data collection sheet

ID	Age	Gender	Group	received allocated Tx	MCDASf 1	MCDASf 2-1	MCDASf 2-2	Houpt 1	Houpt 2	Tx outcome	Type of Tx

Appendix I E4 wristband data collection sheet

ID	HR 1 baseline	HR 1 highest	ST 1 baseline	ST 1 lowest	HR 2 baseline	HR 2 highest	ST 1 baseline	ST 2 lowest

Appendix J Child participant questionnaire for the study group

UNIVERSITY OF LEEDS
School of Dentistry

The Leeds Teaching Hospitals NHS
NHS Trust

IRAS project ID: 270932

V:3

Participant Code: ____

PATIENT QUESTIONNAIRE (AGES 5-15)

Please circle the number that best describes your response. Your mum, dad or guardian can help you answer.

1) How did the wristband feel?

0 Uncomfortable ***1 Comfortable*** ***2 No difference***

2) How did trying on the nose piece and magic gas make you feel before the second visit?

0 Less relaxed ***1 More relaxed*** ***2 No difference***

3) Is it a good idea to try on the nose piece and the magic gas before treatment on the first visit or not?

0 No ***1 Yes*** ***3 Don't know***

Thank you for your feedback

Appendix K Child participant questionnaire for the control group

UNIVERSITY OF LEEDS
School of Dentistry

The Leeds Teaching Hospitals NHS
NHS Trust

IRAS project ID: 270932

V:3

Participant Code: [ ]

PATIENT QUESTIONNAIRE (AGES 5-15)

Please circle the number that best describes your response. Your mum, dad or guardian can help you answer.

1) How did the wristband feel?

0 Uncomfortable *1 Comfortable* *2 No difference*



2) How do you think that trying on the nose piece and magic gas would make you feel before the second visit?

0 Less relaxed *1 More relaxed* *2 No difference*



3) Is it a good idea to try on the nose piece and the magic gas on the first visit before treatment or not?

0 No *1 Yes* *2 Don't know*



Thank you for your feedback

Appendix L Parent questionnaire for the study group

UNIVERSITY OF LEEDS
School of Dentistry

The Leeds Teaching Hospitals NHS
NHS Trust

IRAS project ID: 270932

V:2

Participant Code: [ ]

PARENT QUESTIONNAIRE

Please circle ◯ the number that best describes your response.

1) How do you think that trying on the nose piece and relaxation gas made your child feel before the treatment visit?

0 Less relaxed ***1 More relaxed*** ***2 No difference***

2) Is it a good idea for the children to try on the nose piece and the relaxation gas before treatment on the first visit or not?

0 No ***1 Yes*** ***3 Don't know***

Thank you for your feedback

Appendix M Parent questionnaire for the control group

UNIVERSITY OF LEEDS
School of Dentistry

The Leeds Teaching Hospitals NHS
NHS Trust

IRAS project ID: 270932

V:2

Participant Code: [ ]

PARENT QUESTIONNAIRE

Please circle ◯ the number that best describes your response

1) How do you think that trying on the nose piece and relaxation gas would make your child feel before the treatment visit?

0 Less relaxed *1 More relaxed* *2 No difference*

2) Is it a good idea for the children to try on the nose piece and the relaxation gas before treatment on the first visit or not?

0 No *1 Yes* *2 Don't know*

Thank you for your feedback