Bioethical Issues in Conducting Pediatric Dentistry Clinical Research

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Pediatric clinical research on new drugs and biomaterials involves children in order to create valid and generalizable knowledge. Research on vulnerable populations, such as children, is necessary but only admissible when researchers strictly follow methodological and ethical standards, together with the respect to human rights; and very especially when the investigation cannot be conducted with other population or when the potential benefits are specifically for that age group. Clinical research in Pediatric Dentistry is not an exception. The aim of the present article was to provide the bioethical principles (with respect to the child/parents' autonomy, benefit/risk analysis, and distributive justice), and recommendations, including informed consent, research ethics committees, conflict of interest, and the "equipoise" concept. Current and future worldwide oral health research in children and adolescents must be conducted incorporating their perspectives in the decision-making process as completely as possible. This concept must be carefully considered when a dental clinical study research is going to be planned and conducted, especially in the case of randomized controlled trials, in which children will be recruited as participants.

Key words: *Bioethical, Child, Clinical Research, Randomized Controlled Trial.*

INTRODUCTION

Clinical research ethics constitutes the systematic consideration of moral and ethical problems arising when conducting an investigational study on humans, and jointly its potential consequences, as an interface between science and society.[1] In health-science clinical research, children must be viewed as vulnerable subjects who should be fully protected from the risks of the research process.[2,3] This type of clinical investigation generates useful information for developing novel and better therapeutic strategies to be proposed for the management of specific disorders primarily affecting dental pediatric patients (*e.g.* dental caries and its rehabilitative management).[1,4,5] According to the *International Ethical Guidelines* for health-related research involving humans, the participation of children is indispensable for research into diseases or abnormal conditions of childhood to which they are particularly susceptible, as well as for clinical trials that have not previously rigorous tested in this group age.[6]

Contemporary pediatric research, including of course the pediatric dentistry science, should be mostly conducted *with* children rather than *on* children -"*what adult think children think*", assuming the superiority of adult knowledge-, a modern concept known as *child-centered-research* (ChCR).[7-9] Nowadays, children's opinions about what matters to them should be considered by health researchers; besides, they deserve to be involved in different stages during the research process.[8] According to this, basic principles of ChCR are: (i) Children should be much more active participants throughout the research process; (ii) They have a voice and what they say should be taken seriously on account; (iii) They can be competent and reflexive in reporting their own experiences; and, (iv) Rather than researching on children, working for and with them, as earlier stated.[7,10]

In order to provide the best clinical oral care to children, it is necessary, therefore, to use the best available evidence on therapeutic effectiveness of different dental procedures and materials to take appropriate treatment decisions.[7,11,12] Thus, researchers should validate the efficacy and safety of their tested materials or procedures for possible future application in the clinical setting. The clinical research process is open to abuse in many forms; an investigation may be unethical when it involves attacks in any way against the experiment participants.[1,13] One example of unethical behavior from pediatric dentistry clinical research is the "*Vipeholm* study", developed in 1954, on 436 disabled children with learning problems followed for 5 years while living in an institutionalized setting. Patients were divided into feeding groups in order to test different

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dietary regimens regarding their relative cariogenicity. Researchers not only did not request informed consent from the patients for their participation in the study, but nor did they inform that them that they were participating in an investigation with potential harmful outcomes (dental caries), without any type of care during the observation period.[14] Therefore, human trials are only acceptable when investigators follow fundamental methodological requirements and adhere to strict bioethical principles, constituted mainly in the *Declaration of Helsinki* and other internationally accepted statements (*e.g., The Nuremberg Code, The Belmont Report, The Council for International Organizations of Medical Sciences [CIOMS] guidelines, or The UNESCOS's Universal Declaration on Bioethics and Human Rights*).[15] These guidelines represent frameworks constituted by ethical principles and human rights, addressed to health-related researchers and ethics evaluation committees; these principles have been mainly conceived to minimize risk and maximize the possibility of therapeutic benefit for the pediatric participant.[6,15-17] The majority of countries have recognized these bioethical statements and have also developed regulations or guidelines specific to a sound research with children.[2,10] Pediatric dentistry researchers must strictly respect these ethical standards when planning, conducting, and reporting an Randomized Controlled Trial (RCT) on children, always bearing in mind an appropriate balance between risk and potential benefits to these children, from the experimental procedures to be carried out.[3,11,12]

In this context, the aim of the present article was to provide to pediatric dentistry researchers the fundamental methodological considerations of the randomized clinical trials (RCT) conducted in children; the bioethical principles (child/parents' autonomy, benefit/risk analysis, and distributive justice), and some recommendations, including informed consent, research ethics committees, conflict of interest, and the "equipoise" concept.

Randomized Clinical Trials in Pediatric Dentistry Research

When the issue to be investigated has been plainly identified and the research question formulated, the best methodological design has to be chosen to answer that question.[12] Among the diverse designs employed currently, RCT provides the highest level of evidence in pediatric clinical research in order to fill information gaps regarding the efficacy and safety of new drugs and biomaterials for employment in humans.[1,12,18] This design offers diverse advantages over other types of studies, such as observational or non-randomized trials, in terms of separating the actual therapeutic effect from effects that may be attributable to another, alternative interventional approach or to a placebo.[19,20] However, along with benefits, there are potential risks and inconveniences for children participating in a RCT, including discomfort, pain, fear and anxiety, separation from parents or the familiar environment, effects on growing or developing organs, and size or volume of biological samples.[21]

Well-conducted RCTs aim at ensuring that pediatric patients will eventually benefit by receiving the best clinical management through efficacious treatments;[3,12,18] unfortunately, many prescribed therapies for children have not been adequately tested in children, sometimes resulting in harmful treatments being given and beneficial treatments being withheld.[21] So, it is imperative the complete and transparent reporting of a pediatric trial (*e.g.* brief dental literature review, justification –relevance and pertinence–, methodological design, description of participant children, study settings, randomization methods, and tested interventions or procedures). This information helps the relevant findings to be well understood by readers or systematic review developers.[12] To meet this crucial aim, many journals require authors to complete the *Consolidated Standards of Reporting Trials* (CONSORT) reporting checklist, before submitting a paper for review and approval.[12,22] This checklist is constituted by 37 items concerning the indispensable information that must be reported from a well-designed and conducted RCT with a two-group parallel design and random assignment of participants to the study groups.[22] Likewise, from 15 to 20 years ago, the International Committee of Medical Journal Editors have strongly encouraged that medical and dental journals only publish *a priori* registered clinical trials, in a public trials registry at or before the time of first patient enrolment (for example, Clinical Trials.gov), which has important implications for transparency in trials;[12,23] this precept is also recommended by the World Medical Association's *Ethical Principles for Medical Research Involving Human Subjects* –item 35–.[17]

On the other hand, necessary funding of pediatric clinical trials should be targeted, as above mentioned, to fill identified gaps in evidence addressed to improve and promote child health. However, much research does not lead to achievements or has relevance for human health; for example, although basic research is as important as clinical research for the human health knowledge, in some cases it is difficult to clearly establish the direct benefits to human health generated from basic research. In other words, some funding sources cannot be justified, and therefore, the transparency of processes by which funders prioritize and decide what research to support should be increased and regulated.[24] In order to appreciate the funding practice currently, it is necessary to consider judiciously the statement from Innes, Schwendicke and Lamont: "*Trials are often carried out with a providence that has more to do with happenstance and interest of the researcher than with efficacy and priority in mind. However, this has been changing in many countries with governments, research councils and charities (the three main funders of public research) identifying areas where evidence is needed and commissioning for them*".[12]

As neonates, infants, children and adolescents have distinctive physiologies and health needs than adults; these populations deserve special bioethical considerations to be carefully taken in account and followed with strict adherence by dental researchers and research ethics committees.

Bioethical Principles in Pediatric Dentistry Research

The main general rationale in any clinical research project with minors is "first, do not harm"; in other words, children must be protected from unnecessary risks of harm.[6] So, throughout the entire process of a clinical trial with minor subjects, researchers and any person involved in the trial must conduct themselves under three key ethical principles:[1,2,7,19,25]

1. *Respect for the autonomy* of children and parents or legal guardians. This means that they need to be informed in detail about the study objectives and the procedures to be carried out, including the risk of potential adverse effects or discomfort entailed. In addition, signed informed consent should be completely voluntary, emphasizing that they are

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at liberty to abstain from participation or to withdraw their consent at any time.

2. *Analysis of benefits and risks* (*beneficence* -doing good-, and *non-maleficence* – do not harm). A previous careful assessment is imperative of the comparison between predictable risks and benefits to the child. No clinical study guarantees the absolute safety of the experimental interventions. Therefore, to minimize the danger of damage and to safeguard the participants' integrity, all trials must be conducted only by scientifically qualified and clinically competent dental researchers. They should also consider that the importance of the trial's aim must be in proportion to the inherent risk to the child.

3. *Distributive justice*. This principle deals with the assurance by the researchers that the benefits and burdens generated during any clinical trial are equitably distributed among child participants, through a fair selection of the study subjects. In other words, the selection process should be carried out and justified for solid scientific or ethical reasons. For example, inclusion and exclusion criteria should not be based upon potentially discriminatory personal characteristics, such as race, ethnicity, economic status, age or sex, unless there are strong reasons to do so; thus, children should not be included or excluded in a study only "in the interest of science and society". In a few instances –around 25% of pediatric trials–, children may benefit from financial retribution, provided that payment does not distort both the parents' and children's decision making.[6,16,21] Additionally, equitable distribution requires that participants be drawn from the population living in the geographic area where the study results can be applied. Diverse models for distributive justice have been proposed according to each participant's equal share, need, effort, social contribution or merit.

In addition to knowing the bioethical principles in clinical pediatric dentistry investigation, researchers need to understand the corresponding normative or legal issues governing these principles, such as the importance of obtaining an informed consent from mature children, parents or legally authorized representatives, and the role of the institutional ethical committees.

Informed Consent

The latest General Assembly of The World Medical Association in Fortaleza, Brazil, in October 2013, has stated, in the Declaration of Helsinki's principle number 25,[17] that: "*Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees".* Thus, any patient possesses the moral and legal right to accept or refuse any proposed medical/dental intervention, except in cases of diminished decision-making capacity.[26] During the consent process in pediatric research, it is mandatory the inclusion of the views of children and young people, by giving them sufficient information and competence over the treatments under study.[8,25] In medical and dental research, informed consent is defined as: "*The voluntary agreement given by a person or a patients' responsible proxy (for example, a parent) for participation in a study, immunization program, treatment regimen, invasive procedure, etc., after being informed of the purpose, methods, procedures, benefits, and risks*".[27,28] Informed consent (or parental permission) should be always freely obtained, preferably in writing, and signed by one or both parents (or legal guardians), by the patient who is able to give the consent, the main researcher, and two independent witnesses.[1,19,28,29]

Children and other vulnerable populations possess a lower decision-making capacity and are generally unable to consent on their own behalf;[26,28-30] thus, adults determine whether the risk-benefit ratio is acceptable in order to permit a clinical trial to go forward, particularly when invasive procedures will be tested;[25,31] this process is known as *proxy consent* or *parental permission.*[21,32] If the potential anticipated therapeutic benefit justifies the risk, namely, with minimal or a minor increase above minimal risk, researchers only need the permission of either parent and the assent of the child, whenever she/he is sufficiently and cognitively competent.[28,29,31,33,34] Child's agreement to participate in an oral research when she/he is not legally certified, or lacks sufficient understanding for giving consent competently, is called *assent.*[21,35] Assent also means that a child as clinical research participant has competence to recognize the nature, risks, and benefits of a study, after a readily understandable explication or by reading a simple form about the study, and then giving her/his verbal choice about whether they want to participate or not.[25,30,36] However, they do not enough competence to give a fully informed consent.[30,32,35,36] It has been established that children aged after eight or nine years develop sufficient maturity and psychological competence to distinguish right from wrong, and thus are capable to asset an intervention, whenever their autonomy is respected.[30,35] Thus, and according to the recent concepts adopted by the CIOMS guidelines number 9 and 17,[6] child assent must be considered as a process, and not merely as the absence of dissent; this process must consider not only the patient age, but also their individual circumstances, life experiences, emotional and psychological maturity, intellectual capabilities, and family situation;[15] likewise, the latest version of the Declaration of Helsinki, in its principles 28 and 29, clearly considers these same issues.[17] In some research institutions, two separate documents are designed: an assent form for children or for adolescents, and a separate form for parental permission; while other institutions employ a two-part structure consent form: one section is specific to be completed by the minor participant, and the other part by the parents.[37] In both cases, researchers should decide if a minor is capable of being involved in the assent process;[30,36] these all concerns on assent from children were first adopted in the UK,[7,10,25,30] and the USA.[36] An excellent and complete guideline on child assent and parental permission in clinical research, which includes diverse informed consent templets, can be found in the website of The UCLA's Office of the Human Research Protection program (OHRPP).[36]

Bartolome has mentioned four crucial components for assessing the child capability to give consent:[38] (i) A developmentally appropriate understanding of the nature of the condition; (ii) Disclosure of the nature of the proposed intervention and what it will involve; (iii) An assessment of the child's understanding of the information provided and the influences that impact on the child's evaluation of

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the situation, and (iv) A request for the child's expression of willingness to accept the intervention. Lists of matters that must appear, with full explanation, in a dental-research informed consent can be consulted in the *Guideline on Informed Consent* (under the subtitle "Recommendations"),[28] Additionally, the AAPD recommends to obtain a separately consent, when pharmacologic or invasive behavioral procedures (for example, sedation, general anesthesia, protective stabilization/immobilization, hand-over-mouth technique) are indicated during the clinical phase of a research.[28]

Informed consent should be considered as the most fundamental ethically and medico-legal component of any clinical investigation.[1,25,30] Finally, the main researcher must clearly state that patients and parents are free to refuse or withdraw their consent to participate at any time, without compromising their health-service benefits or without interfering with the dentist-patient relationship.[1,4,25,39] An excellent example of child-centered research and how to apply an informed consent in pediatric dentistry research, can be seen in the clinical study of Rodd et al., about the potential physical and psychological consequences of general anesthesia, from a child's perspective.[40]

Research Ethical Committees

Children should not be enrolled in a clinical investigation unless it is scientifically necessary to achieve important information on therapeutics concerning the social or particular oral health and welfare of children.[2] Universities, hospitals, research institutes, non-governmental organizations, and pharmaceutical/medical/dental corporate entities where human (and animal) experimental investigations are carried out (which involve cadavers, biological fluids, embryos/fetuses, interviews/surveys/questionnaires, and data confidentiality, among others) are obliged to create and maintain an independent Research Ethics Committee (REC) or Institutional Review Board. RECs scrutinizes investigation protocols for compliance with international ethical and scientific regulations before their implementation on human beings.[4] All of these concerns have been clearly stated in the latest version of the Declaration of Helsinki, in its principles numbers 22 and 23,[17] and in the guideline 23 of the CIOMS.[6]

The REC must be transparent in its functioning and independent of researchers, sponsors, and any other undue external influence. Furthermore, it must take into consideration the laws and regulation of the country in which the research is to be performed. In some countries, for example, the USA, the REC not only approves the trial protocol, but it is supposed to monitor compliance with bioethical standards during the entire investigation process and to detect any potential transgression with regard to participants or another inadequate actions. However, in the UK, these ethic committees are not responsible for proactive monitoring the trials compliance; this task corresponds usually to the study's sponsor and the employing organization, especially for concerns regarding to safety reporting (*e.g.* adverse effects), notification of urgent safety measures and notifications of the conclusion or early termination of a trial.[39]

Researchers who intend to conduct a clinical trial must provide the committee with an investigation protocol for its in-depth review.[17] This document should be clear and thoroughly explain all determining aspects of their project as follows: the design; a brief literature review; the study justification (relevance and pertinence), and the procedures and methodological characteristics of an RCT involving pediatric patients, some of these related with bioethical issues (*e.g.*, randomization method, use of a placebo as control, appropriate sample size, blinding, concealed assignment strategy, and informed consent).[4,41] Additionally, the research protocol must include information about the feasibility of the investigation, funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for children, and information regarding the safety of the study site, medical monitoring and provisions for treating and or compensating harms as a consequence of participation in the study.[6,17]

The first duty of a REC is to ensure that child rights are vigorously and effectively protected during the research process, and also that the associated risks are reasonable in relation to the potential benefits and knowledge to be gained.[6,16,21] Therefore, a committee should be duly qualified and integrated in a multidisciplinary manner: at least two competent members with training and experience in research methods; two members knowledgeable in bioethics and/or law; one lay person, and one or two members with the special expertise required by the protocol-under-review.[1,4,16,17,41] In cases of clinical trials with children, the committee should be advised by a scientist with pediatric expertise in the design, review, and conduct of studies involving children.[21] Thus, there is a less possibility of inadvertently permitting research in children that would not be allowed under better circumstances.[16] In addition to giving advice, the essential tasks of an REC are always the following: to preserve, first, the patient's autonomy second, the right of children to safeguard their mental/physical integrity along the trial, observing good clinical practices; thus, and according to the Declaration of Helsinki, the committee have the right to strictly monitor ongoing studies.[42] Any amendment to the original protocol proposed by the researchers or sponsors must be carefully reviewed and approved by the REC; also, the researchers are obligated to report all the pertinent information regarding any serious adverse events. And third, to maintain privacy/confidentiality with regard to the data generated on the patient to avoid personal identification.

Ethical review is the responsibility, whenever possible, of every institution that participates in a clinical trial, as in the case of *multicenter* studies.[20] Other important roles for the REC are the following:[1,6] (i) Promotion of research with social value, protection of researchers, and the maintenance of academic freedom; (ii) Punishment of fraud and abuse (*e.g.*, plagiarism or selective reporting); (iii) Compensation for injuries; (iv) Reviewing/preventing non-equity or discrimination during the patient selection process for a clinical study, and (v) Prevention of conflicts of interest.

Pediatric dentistry researchers should consider other crucial ethical concepts when planning, conducting and reporting a clinical investigation that involves children and adolescents. For example, the conflicts of interest communication process and the equipoise principle concept.

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Conflicts of Interest

According to Barnett, a conflict of interest is "*a set of conditions in which professional/scientific judgment concerning a primary interest (e.g. patient's welfare or validity of a research) tends to be unduly influenced by a secondary interest (e.g., financial gain)*". Therefore, the complete and transparent reporting of potential conflicts of interest, financial or non-financial is an ethical obligatory requirement by researchers when publishing their findings.[12,41] Some examples of potential or real conflicts of interest related with bioethical concerns in pediatric dentistry can be noted:[43]

- A dental investigator who developed a newly marketed restorative material for primary molar cavities might unconsciously give greater emphasis to this material than to alternative and effective competitive products in publications, conferences, scientific forums, or lectures, meriting attention by faculty or research-institution members.
- Another investigator has devoted significant time and effort to promoting a well-grounded theory regarding the dental pulp physiology of young permanent teeth, thus gaining a considerable reputation; however, she/he then falls into strong intellectual biases solely to protect or to maintain that theory current, even without receiving financial incentives.
- An investigator improperly reports her/his study findings, clearly intending to promote a specific product or company: (i) Data falsification; (ii) Selective reporting -emphasis of positive results while ignoring the less favorable ones-; (iii) Lack of balance when findings are published, supporting a particular product, and (iv) Designing deliberate rather than objective research protocols to produce results in favor of a sponsoring company's product.
- When dental investigators: (i) Are involved in the development and commercialization of their discoveries; (ii) Serve as REC members, consultants, speakers, or investigators for specific companies, or (iii) Hold important equity positions in a company that is dependent for survival on the product's success.

The "Equipoise Principle" Concept

An essential bioethical requirement for an RCT is the *equipoise principle*, which consists of two main components. First, the genuine uncertainty of knowing, prior to beginning the trial, whether either study intervention arm (experimental or control) is superior to the other; if there is published evidence that one treatment is the better choice, this therapy will be withheld from some children while receiving the other.[2,19] Second, the ethical norm of "none of enrolled patients will take an inferior treatment" -sometimes mentioned as the *duty of care* concept- namely, the best actively controlled comparator (the *standard of care*), instead of a placebo; thus, and according to the *Declaration of Helsinki*, placebo would be admissible in only two research scenarios: in cases in which an established treatment or procedure is not available or known,[19] and when it is necessary to determine the efficacy or safety of a new intervention and the patients who receive placebo (or no treatment) "will not be subject to any risk of serious or irreversible harm".

FINAL COMMENTS AND CONCLUSIONS

Pediatric clinical research had led to several notable and often unexpected advances in the protection and promotions of infants and children health worldwide.[24] The United Nations Convention on the Rights of the Child (UNCRC) recognizes that children's views, perspectives, desires, and expectations should be respected and taken seriously to all matters affecting them, including health care and research. Therefore, dental investigation practitioners must consider the already suggested and advocated concept of *child-centred-research*, in which children are active participants rather than objects during the research development, and so, they can contribute to improve the oral health care process, through valuable information.[8] The present work, as an opinion piece, has reviewed bioethical issues that must be strictly borne in mind when child participants are enrolled in a dental clinical trial, in order to protect their pertaining human rights, regardless of where the trial is conducted, whenever crucial bioethical issues are strictly followed.[2,4] Together with the implementation of good clinical and safe practices, adequate management of conflicts of interests and investigator integrity, the application of bioethical dental research's high-standard principles may guarantee the generation of sound, necessary, and validated oral clinical therapeutic evidence, to the benefit of our children and other vulnerable populations.

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REFERENCES

1. Gibbons DE. Medical and dental research. In: Lambden P, ed. Dental law and ethics. Oxon, UK: Radcliffe Medical Press; 2002.
2. Roth-Cline M, Gerson J, Bright P, Lee CS, Nelson RM. Ethical considerations in conducting pediatric research. Handb Exp Pharmacol; 205: 219–244, 2011.
3. Marshman Z, Innes N, Deery C, et al. The management of dental caries in primary teeth–involving service providers and users in the design of a trial. Trials; 13: 143, 2012.
4. Ellen RP, Singleton R. Human rights and ethical considerations in oral health research. J Can Dent Assoc; 74: 439a–439e, 2008.
5. Innes NPT, Clarkson JE, Speed C, Douglas GVA, Maguire A, FiCTION Trial Collaboration. The FiCTION dental trial protocol – filling children's teeth: Indicated or not? BMC Oral Health;13: 25, 2013.
6. International Ethical Guideline for Health-related Research Involving Humans. 4th. Ed. Geneva, Switzerland. Council for International Organizations of Medical Sciences (CIOMS); 2106.
7. Marshman Z, Hall MJ. Oral health research in children. Int J Paediatr Dent;18: 235–242, 2008.
8. Marshman Z, Gupta E, Baker SR, et al. Seen and heard: Towards child participation in dental research. Int J Paediatr Dent; 25: 375–382, 2015.
9. Wallace A, Rogers HJ, Zaitoun H, Rodd HD, Gilchrist F, Marshman Z. Traumatic dental injury research: On children or with children. Dent Traumatol; 33:153–159, 2017.
10. Marshman Z, Gibson BJ, Owens J, et al. Seen but not heard: A systematic review of the place of children in 21st-century dental research. Int J Paediatr Dent; 17: 320–327, 2007.
11. Marshman Z. 'The voice of the child in the oral health research' (Guest Editorial). Int J Paediatr Dent; 25: 309, 2015.
12. Innes NPT, Schwendicke F, Lamont T. How do we create, and improve, the evidence base? Brit Dent J; 220: 651–655, 2016.
13. Mehnaz-Mirza A. Importance of informed consent in dentistry. Int Dent J Stud Res; 1: 13–16, 2012.
14. Gustafsson BE, Quensel CE, Lanke LS, et al. The Vipeholm dental caries study; the effect of different levels of carbohydrate intake on caries activity in 436 individuals observed for five years. Acta Odontol Scand; 11: 232–264, 1954.
15. van Delden JJM, van der Graaf R. Revised CIOMS International Ethical Guidelines for Health-realted Research Involving Humans. J Am Med Assoc (published on line, December 2016):E1-E2. Doi: 10.1001/jama.2016.18977.
16. Yan EG. Munir KM. Regulatory and ethical principles in research involving children and individuals with developmental disabilities. Ethics Behav; 14: 31–49, 2004.
17. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. J Am Med Assoc; 310: 2191–2194, 2013.
18. Emanuel EJ, Wendler D, Grady Ch. What makes clinical research ethical? JADA; 283: 2701–2711, 2006.
19. Henschel AD, Rothenberger LG, Boos J. Randomized clinical trials in children–Ethical and methodological issues. Curr Pharm Des; 16: 2407–2415, 2010.
20. Hujoel PP. Levels of clinical significance. J Evid Base Dent Pract; 4: 32–36, 2004.
21. Caldwell PHY, Murphy SB, Butow PN, Craig JC. Clinical trials in children. Lancet; 364: 803–811, 2004.
22. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomized trials. BMJ; 340: c869, 2010.
23. International Committee of Medical Journal Editors. Clinical Trial Registration. Available at: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. Accessed on November 3, 2016.
24. Chalmers I, Bracken MB, Djulbegobic B, et al. How to increase value and reduce waste when research priorities are set. Lancet; 383: 156–165, 2014.
25. Gilchrist F, Rodd HD, Deery C, Marshman Z. Involving children in research, audit and service evaluation. Br Dent J; 214: 577–582, 2013.
26. Katz AL, Webb SA; COMMITTEE ON BIOETHICS. Informed consent in decision-making in pediatric practice. Pediatrics; 138, 2016.
27. The free dictionary (by Farlex). http://medical-dictionary.thefreedictionary.com/informed+consent. Accessed on April 11, 2016.
28. American Academy of Pediatric Dentistry. Clinical practice guideline: Guideline on informed consent. Pediatr Dent (Reference manual); 37: 95–97, 2015-16.
29. Hein IM, De Vries MC, Troost PW, Meynen G, Van Goudoever JB, Lindauer RJL. Informed consent instead of assent is appropriate in children from the age of twelve: Policy implications of new findings on children's competence to consent clinical research. BMC Med Ethics; 16: 76–82, 2015.
30. Shaw C, Brady LM, Davey C. Guidelines for research with children and young people. National Children's Bureau. London, UK; pp. 27–33, 2011.
31. Leventhal N, Tarini B, Lantos J. Ethical issues in neonatal and pediatric clinical trials. Pediatr Clin North Am; 59: 1205–1220, 2012.
32. Foreman DM. The family rule: A framework for obtaining ethical consent for medical interventions from children. J Med Ethics; 25: 491–496, 1999.
33. Roth-Cline M, Nelson R. Parental permission and child assent in research on children. Yale J Biol Med; 86: 291–301, 2013.
34. Cerda-Cristerna BI, Garrocho-Rangel JA, Pozos-Guillén AJ. El consentimiento informado en la investigación clínica en Estomatología. ADM; 71: 301–305, 2014.
35. Kaushik JS, Narang M, Agarwal N. Informed consent in pediatric practice. Indian Pediatr; 47: 1039–1046, 2010.
36. University of California in Los Angeles (UCLA). Office of the Human Research Protection Program. Guidance and procedures: Child assent and permission by parents or guardians. http://ora.research.ucla.edu/OHRPP/Documents/Policy/9/ChildAssent_ParentPerm.pdf. Last updated: June 9, 2016. Acceded on September 29, 2016.
37. UK Data Archive. Available at: http://www.data-archive.ac.uk/media/112616/ukdaconsentchild.pdf. Acceded on October 15, 2016.
38. Bartolome W. Ethical issues in pediatric research. In: Vanderpoon H, ed. The ethics of research involving human subjects. Fredrerick, MD: University Publishing Group; 1996.
39. UK Health Departments. Research Ethics Service. Standard operating procedures for research ethics committees. Version 7.1, October, 2016. Available at: http://hra.nhs.uk/documents/2016/10/res-standard-operating-procedures-version-7-1.pdf.
40. Rodd H, Hall M, Deery C, Gilchrist F, Gibson BJ, Marshman Z. 'I felt weird and wobbly'. Child reported impacts associated with a dental general anaesthetic. Br Dent J; 216: E17, 2014.
41. Cerda-Cristerna BI, Garrocho-Rangel JA, Pozos-Guillén AJ. Comité de Ética en Investigación: La consciencia del investigador para la protección del sujeto participante en una investigación clínica en Estomatología. ADM; 71: 256–260, 2014.
42. ICH Practice Guidelines. Available at: http://www.ich.org/products/guidelines.html. Accessed on April 8, 2016.
43. Barnett ML. University-industry relationships in dentistry: Past, present, future. J Dent Educ; 66: 1163–1168, 2002.

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