Ethical Concerns of Dentistry and Pharmacy Research Protocols in Egypt: An Institutional Review Board Perspective

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Introduction

Research is crucial for improving clinical practice [1], and it emphasizes respect for humans through informed consent and information provided to the participants.[2,3] Dental research participants may encounter a number of risks, such as wide variability within and between subjects. The site in the mouth, specialty, and the clinic performing the procedure may pose different risks.[4] Risk can be defined as "the probability that a particular mishap or an unwanted effect will occur within a given period of time".[5] Weighing risks versus benefits can be subjective in several instances, even in simple everyday procedures. The simplest example is the pain control using anesthesia for caries excavation in dental clinical care, regardless high pain tolerance that some patients do have. [6]

Experimental gingivitis is induced by refraining from oral hygiene for 21 days. It was first introduced as a research method in 1965 [7], and researchers continue to use it in contemporary research.[8] The field of radiography has witnessed a significant breakthrough with the introduction of CBCT, which is more accurate and less expensive than CT scans and still entails lower radiation hazards.[9,10] CBCT has become the new standard of care.[10,11] However, clinicians should be aware that the radiation dose of CBCT is higher than that of conventional radiographic techniques.[12] Hence, understanding the radiation dose delivered to the patient is a safety concern, as the biological effects of these ionizing radiations include tissue reactions and chromosomal effects.[13]

Prosthetic restoration of missing teeth using implants has become a standard treatment. However, research to guarantee high success rates and shorter healing times is based on using less-invasive surgical techniques, providing good evidence to support the benefit, and evaluating risk factors and potential complications that could lead to implant failure.[14]

Microabrasion is a simple, inexpensive means for the esthetic management of superficial intrinsic enamel discolorations and defects.[15,16] It employs a combined chemomechanical conservative approach to remove the porous outer enamel surface and trapped stains. Thus, it is the least invasive of all esthetic procedures.[16-19] The technique is safe and can be used with tooth bleaching in teeth with persistent discoloration.[15] However, some risks still exist. Since early on, Dalzell et al. emphasized the critical effect of the pressure used during the microabrasion procedure.[20] The higher the pressure applied, the more enamel is removed.[20-22] Multiple studies have found that the hypothetical enamel wear of the microabrasion technique is multifactorial, which includes the type, concentration, and pH of the acid used, abrasive medium, application mode, force applied, time of instrumentation, and revolutions per minute.[23,24]

Intrinsic stain reduction chemically using carbamide peroxide and hydrogen peroxide, at different concentrations, depending on the product or protocol.[25] Carbamide peroxide releases hydrogen peroxide, a powerful oxidizing vehicle.[26] Bleaching occurs when reactive oxygen molecules from hydrogen peroxide oxidize the organic chromophores within enamel and dentin.[27] The most unfavorable bleaching effect is tooth sensitivity, which may be more common when higher concentrations of active agents are used. Typically, the hypersensitivity is mild and temporary[28] and usually occurs with all forms of bleaching.[29]

Dental specialties use lasers for photochemical effects, photoablation, tissue fluorescence, and vaporization.[30] Laser use has many benefits resulting in the reduction of fear,

anxiety and postoperative complications. [31] However, light energy from a laser beam causes tissue interactions with target cells.

Advances in medical technology have resulted in an updated definition of a biomedical material as "any substance that is engineered to take a form, which either alone or as part of a complex system, interacts with components of living tissue to direct the course of any therapeutic or diagnostic procedure".[32] All biomaterials used in dentistry should be tested for biocompatibility using various screening tests to ensure that they are safe and pose no hazard to human health. The biocompatibility test necessitates a four-phase evaluation of new materials: general toxicity, local tissue irritation, preclinical evaluation, and clinical evaluation.[33,34] Before comprehensive animal experiments and clinical trials, the new materials must be assessed using initial cytotoxicity and secondary tissue screening tests. Test results should be constantly reviewed and interpreted considering the material.

Extracted teeth are a valuable biological material source that is indispensable for dental research.[35] To obtain reliable results, the teeth samples or whole teeth should be properly prepared and stored under biologically safe conditions representing the natural tooth condition without affecting its mechanical and chemical properties. The tooth must also be sterilized or disinfected with chemical solutions or various inactivating means before use to eradicate pathogens.[36]

IRBs are crucial in protecting participants and guiding researchers to ethically conduct research. The role of the IRB in reviewing dental and pharmacy research protocols cannot be overstated. Most research ethics committees in Egypt have been operating for the past 15 years. In 2007, 2009, and 2010, the National Research Institute in Egypt trained Oral and Dental Medicine Faculty members in Alexandria, Cairo, and Tanta to establish their research ethics committees.[37] An Egyptian-Saudi knowledge, attitudes and practice (KAP) survey showed evidence that faculty members in dental schools included in the survey were poorly informed

about ethical principles and the role of IRBs. More and above, the survey indicated that the respondents' knowledge was irrelevant to whether they received training or not.[38] Another multicenter survey in several Medical Sciences faculties in Egyptian universities, found out that although a high percentage of respondent held a favorable opinion about IRBs, still about one third considered the IRBs as a research-delaying obstacle, and many researchers lacked research ethics training.[39] A later Egyptian study in 2013, highlighted additional concerns, including financial resources, gender representation in the committee, and lack of governmental regulations at that time.[40] This study also revealed the lack of experience of the researchers in protocol writing and study methodologies, which puts more responsibility on Egyptian IRBs to scrutinize the protocols review for participants' protection. Similarly, a KAP survey in India revealed modest knowledge and practice but a positive attitude toward ethics in dental research.[41] Furthermore, a review of ethical issues in dental clinical research publications in Iran reported that only half of the articles mentioned informed consent, whereas only about one-third mentioned discussing the safety of the study with the participants. Obtaining approval from an ethical committee was not mentioned in more than 80% of the papers. Whether the ethical items were omitted in the manuscript but included in the study remains unanswered.[6] Similarly, in 2019 an article was published reporting Ethical Issues in Human Subject Articles Published in Iranian Medical Journals: 2009-2013 and their frequencies.[42]

Misr International University (MIU) is a private university on the outskirts of Cairo, established in 1996. The Faculty of Pharmacy initiated student enrollment in 1997, and the Faculty of Oral and Dental Medicine enrolled their first students in 2001. During the 2013–2014 academic year, faculty members were recruited and trained in research ethics and ethics committee procedures to establish the MIU IRB. The MIU IRB has a Federal Wide Assurance for Protection of Human Subjects (hhs.gov/ohrp/register-irbs-and-obtain-fwas/fwas/fwa-

protection-of-human-subjecct/index.html), that is regularly renewed and follows the guidelines from the Declaration of Helsinki and the World Health Organization.[43-45] The written standard operating procedures of the IRB dictate its composition and functions. From the beginning of the 2014–2015 academic year, on the instructions of the MIU administration, all protocols from the faculties of pharmacy and oral and dental medicine at the university are reviewed first by the research committee to validate the study design and scientific merit and then by the IRB for ethical concerns. The MIU assigns one reviewer for each new protocol; however, all members read all protocols for a detailed discussion in a monthly full board meeting. After obtaining IRB approval, all research protocols must be registered on the MIU account on "clinical trial.gov," which serves as an external evaluator.

Being active for 7 years, the MIU IRB faced some challenges, similar to other universities in the region as highlighted in several studies. [37,39,40] As aforementioned, several publications discussed IRB concerns in Egypt, yet, this is the first to our knowledge to target ethical concerns encountered by the IRB while reviewing dental and pharmacy protocols.

Given the challenges of implementing a new ethical review process, as outlined above, this study aimed to review all protocols handled by the MIU IRB from 2014 through 2021, and ,described the ethical concerns raised during the evaluation of dental and pharmacy research protocols . The results from this review are expected to provide other IRB committee members with the MIU IRB review experience about the ethical challenges and risks determination process. We also aimed to offer recommendations for minimizing risks of research protocols to protect human subjects and improve the quality of research outcomes.

Methods

This observational study is a review of research protocols submitted to the MIU IRB, was designed to describe the ethical concerns of the IRB while reviewing the protocols submitted from the 2014–2015 academic year through December 2021.

As per international regulations (hhs.gov/ohrp/register-irbs-and-obtain-fwas/fwas/fwa-protection-of-human-subjecct/index.html), the MIU IRB comprises nine members, including the IRB Chair and Vice Chair.[46] The committee has gender diversity, and is multidisciplinary with members from the dental, pharmacy, and medical professions, with one non-affiliated member and one member whose primary concerns are nonscientific. The members include two Professors, two Associate Professors, three Assistant Professors and one scientist. The Chair and external member have been on the committee ever since its establishment, while other members in the range of one to four years.

The IRB adopted a three-reviewer system. The Chair and the scientist, in addition to one primary reviewer, read the submitted protocol. All other members are encouraged to read all the protocol, as well. The primary reviewers present a summary the protocol in the meeting, then highlight their comments. The other members then share their comments and discuss the concerns. After voting, the protocol is either approved as submitted, or modifications are required, or deferred usually for lack of sufficient information to make a determination, or rarely refused.

A "human subject determination" is also done to categorize the protocol as protocol involving human subjects or not. If a human subject protocol falls under one of the exemption categories (hhs.gov/ohrp/register-irbs-and-obtain-fwas/fwas/fwa-protection-of-human-subjecct/index.html), the protocol does not have to come back to the committee after its approval.[43] Exempt protocols are those that are of minimal risk to participants and fall into one of the exemption categories, which include education research, surveys and interviews in adults, benign behavioral interventions, retrospective analysis of identifiable samples, or taste and food evaluation studies. For nonexempt protocols the level of risk is also determined, and could be minimal or more than minimal risk.

The MIU IRB members re-read all submitted protocols and highlighted the implied ethical problems. They also reviewed the meeting minutes and decision letters with the required recommendations and modifications, as well as retrieved discussion points. Thereafter, they researched each point according to their specialty, and discussed it with the board before writing their assigned section of this manuscript. There was no questionnaire used in this review, but IRB members were instructed to find out from the protocols and the meeting minutes, the risks in each protocol and write them down. Another member, reviewed all protocols one more time to make sure all points that warranted discussions for risk assessment were retrieved.

Statistical Analysis

Qualitative data were presented as frequencies and percentages. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. This manuscript encompasses all major concerns and minor procedures that warrant discussion for risk-level assessment, no matter how trivial they seemed.

Results

From the beginning of the 2014–2015 academic year to December 2021, 134 protocols were submitted for the IRB review. Of these 134 protocols, 74 (55.2%) involved human subjects, and 60 (44.8%) were "nonhuman subject" protocols. All human subjects' protocols required informed consent procedures; among these, 13 (17.6%) had more than minimal risk, 18 (24.3%) had minimal risk, and 43 (58.1%) were exempt. The more than minimal risk protocols involved six surgeries, including four implants, two new dental materials and two protocols including experimental gingivitis; three protocols included procedures that could cause pulp exposure. The minimal risk protocols included four bleaching protocols, and 14 surveys. The 43 exempt protocols included extracted teeth in 41 protocols, while one was a case report and another was educational (Table 1). Ten (16.7%) of the total submitted

nonhuman subject protocols were from the Faculty of Pharmacy, involving chemical synthesis and analysis of preexisting materials (Figures 1 and 2). The minimal risk and exempt protocols raised a few questions. All protocols were approved after modifications, except for one clinical trial that was rejected due to insufficient preclinical information.

Table 1. Procedures Involved in the Protocols Reviewed by MIU IRB 2014-2021 According to the Type of Risk

Type of Risk Procedure	More than Minimal Risk N=13	Minimal Risk N=18	Human Exempt N=43
	Surgery n=2	Surveys n=14	Extracted teeth n=41
	Implants n=4	Bleaching and microabrasion n=4	Laser* n=6
	Experimental Gingivitis n=2	-	Case report n=1
	Pulp exposure n=3	-	Education n=1
	New materials n=2	-	-

*Laser was done on extracted teeth

†N = total number of protocols in the risk determination category

‡n= number of protocols of each procedure/risk

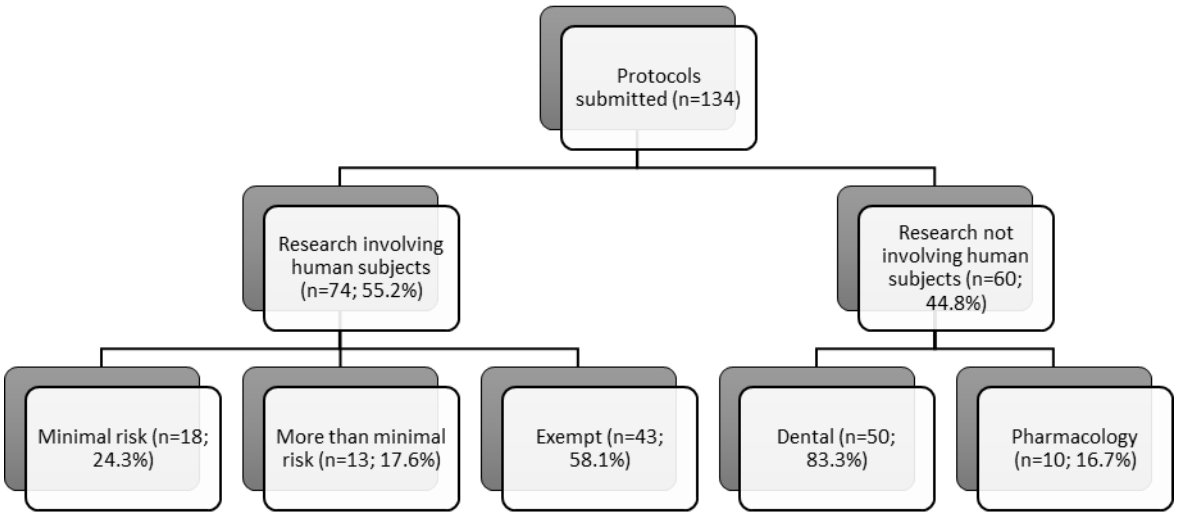

Figure 1. Number and Determination of the Types of Protocols Reviewed by the MIU IRB from the Beginning of the 2014–2015 Academic Year to December 2021.

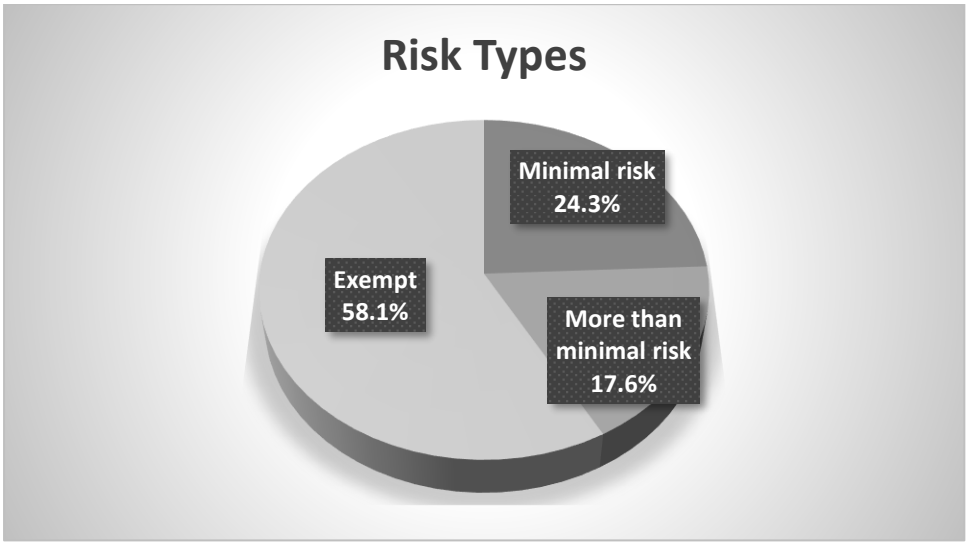

Figure 2. Distribution of Human Subject Protocols (n = 74) According to the Type of Risk.

Discussion

In this review, we aimed to identify ethical issues and concerns that arose during the MIU IRB discussions of dental and pharmacy protocols from 2014-2021.

Notably, the number of clinical trial protocols submitted to the IRB constituted only a small fraction of the protocols. Despite their importance, clinical trials take a long time to complete, and master's students have limited time to complete their research before graduation; MIU still does not have a PhD Program in Dentistry or pharmacology. A few staff members, though, perform clinical trials, but on a small scale. To increase the number of clinical trials, the MIU IRB supports researchers throughout the research process by hosting annual training workshops, including how to write research protocols, and informed consent. Furthermore, researchers are advised to include patient-reported outcome measures in their data collection process, whenever possible, to systematically enhance the value of the research and follow-up on patients' complaints or opinions.

The ethical concerns and issues identified in this review were divided into dentistry and pharmacy protocols.

Dentistry Human Subjects Protocols

Informed Consent Language and Content

The Arabic translation of informed consent forms is a concern that arose during the protocol review. According to the basic principles of research, ethics is respect for the person and granting the right of autonomy, guaranteed by signing an informed consent form that provides adequate information about the risks, benefits, and treatment alternatives to support patients in making a rational decision regarding a specific dental procedure.[47] One main factor in ensuring the validity of informed consent is intelligibility; the consent must be written in a comprehensible, simple, and straightforward language without complex jargon.[48,49] Unfortunately, this requirement is sometimes overlooked, and patients may end up signing a document they hardly understand. This is common in less-developed countries with high rates of poverty and illiteracy.[50,51]

An additional difficulty occurred due to the complex dental terms and procedures that must be translated into Arabic. A valid informed consent form should be prepared in the subjects' native language.[52] Thus, informed consent forms should be translated into Arabic in Egypt, where Arabic is the official language, and only less than half of the population speaks English.[53] This applies to the nonmedical and medical parts of the document, including abbreviations. Dentistry has established itself in most Arab countries, including Egypt, and is taught in English. Attempts to Arabize dental education and terminology have not been fruitful due to the dominance of English as the official language of dental conferences and journals.[54] Several dental terms have no one-to-one equivalent words in Arabic. Thus, long phrases used to explain a dental term rendered the informed consent form ambiguous and incomprehensible even for dental practitioners, members of the IRB.[55]

Sometimes, Arabic translations of the informed consent forms of the protocols were assiduously discussed during IRB meetings to ensure that the Arabized dental terms did not hinder effective dentist–patient communication. In some cases, the IRB recommended holding extended dentist–patient discussions over matters such as risks, benefits, procedures, and alternatives. This recommendation was supported by studies that reported that patients who were allowed post informed consent discussions with their healthcare providers had better understanding and satisfaction of the informed consent and informed consent process.[56-58]

To overcome this language barrier, the MIU IRB requested that the informed consent forms be written in Arabic and then translated to English, instead of written in English and then back-translated into Arabic. This facilitated language comprehension and made the informed consent more understandable. In addition to all members reviewing for other ethical requirements, the IRB relied on the nonscientist and non-dentist members to review the informed consent forms for understandability.

Experimental Gingivitis

The MIU IRB reviewed one protocol using experimental gingivitis. Although experimental gingivitis is reversible and poses minimal risk to patients[7], the IRB was skeptical and required justification for the procedure or a change of study design to avoid the risk of gingivitis and its complications in participants.

Implants

The MIU IRB reviewed four clinical trials for novel implant surgeries, which were all determined to pose more than minimal risk. Extensive discussions of case selection, surgical procedures, sometimes including open sinus procedures, the expected side effects such as infection, swelling, bleeding, and pain and their management, especially implant failure, postoperative care, and patient evaluation and follow-up methods were conducted. Moreover, considering the principal investigators' experience, risks versus benefits were evaluated, and risk minimization options were proposed and discussed to ensure patient safety. Furthermore, the IRB requested the submission of a quarterly report highlighting any adverse effects that may occur.

A key challenge was translating the technical terms to Arabic in the informed consent form, which must provide detailed and comprehensive explanations to the patients regarding the surgical procedures.

Cone-Beam Computed Tomography (CBCT)

The MIU IRB reviewed 19 protocols that included the use of CBCT, which mentioned the effective use of dental CBCT following the safety guidelines and "as low as reasonably achievable" (ALARA) dosage in all protocols.[59-61] The guidelines mandated the justification for CBCT usage. The benefits of using these radiations, e.g., efficient diagnosis and treatment plan or even better therapeutic outcome, should outweigh the potential risk of radiation exposure.

According to the IRB, CBCT must be performed in a licensed facility by a well-trained radiologist. Moreover, a well-trained specialist must conduct the data interpretation and provide an accurate CBCT report to prevent misdiagnosis of the cases and medico-legal issues if a failure occurs. Despite the proven low radiation dose, the IRB recommended limiting its usage to only twice during the whole study: the first time at the start and the second time at the end for the final evaluation to minimize the cumulative exposure effect.

Bleaching and Microabrasion

MIU IRB reviewed four protocols using microabresion and bleaching. Microabrasion risks can be minimized using rubber dam isolation, which protects the gums from direct contact with acid. Furthermore, proper user training is mandatory for standardization of pressure applied. The IRB mentioned these precautions in the protocols that included the microabrasion procedures to decrease the risk for participants.

For bleaching the IRB recommended following common guideline protocols to avoid bleaching sensitivity, such as using nonsteroidal anti-inflammatory drugs and applying 2% sodium fluoride and 5% potassium nitrate gel as a pretreatment.[62,63] The second adverse effect of bleaching may be gingival irritation caused by the bleaching gel coming into contact with the gingiva. This is usually iatrogenic by inadequate application of the protective gel or barrier and ill-fitting trays.[63]

Accordingly, the IRB advised against the use of local anesthesia before bleaching to allow patients to feel any burning sensations as a sign of gel leakage to the gingiva. The investigators' previous training included this mandatory step to prevent iatrogenic drawbacks and increase the effectiveness of the procedure. All bleaching protocols submitted to the MIU IRB were *in vivo* protocols that used different bleaching methods and were considered a minimal risk when the recommended precautions were followed.

Lasers

The MIU IRB reviewed 16 protocols where Laser was used. Although laser in general is safe, it still can be harmful, and could pose a risk to the patients or the operator by direct or reflected light, causing retinal burns.[31] Therefore, the IRB essentially required that the laser be used by qualified personnel. In addition, the protocols must elaborate on laser hazard control measures, e.g., protective goggles, availability of fire extinguishers, and light tight room to protect patients, operators, and auxiliary personnel (https://ehs.mit.edu/wp-content/uploads/Laser_Safety_Guide.pdf).

New Biomedical Materials

One ethical concern of the IRB was the use of new biomaterials in a study, even if they appeared safe and of minimal risk. Any material or device intended for use in humans requires a structured assessment to protect patients from hazards that may result from the unauthorized use of these biomaterials.

The MIU IRB reviewed two research protocols of new dental materials, and carefully followed the International Organization for Standardization (ISO 7405) labeled "The Preclinical Evaluation of Biocompatibility of Medical Devices Used in Dentistry Test Methods for Dental Materials.".[64] Two protocols submitted included the use of new edible materials, a traditional medicinal herb, and a component of a commercially used drug; however, the IRB required preclinical toxicity studies, *in vitro* or in animals, as appropriate.

Dentistry Nonhuman Subject Protocols

Extracted Teeth

The MIU IRB reviewed 40 protocols including extracted teeth. Patients at the MIU Faculty of Oral and Dental Medicine outpatient clinics were routinely requested to provide written informed consent for the retention, storage, and future use of their extracted teeth for research while assuring that the teeth would be anonymously preserved. According to pre-

2018 common rule exemption categories, the IRB determined research involving extracted human teeth as exempt category 4. With the new common rule, the IRB changed the determination to be non-human research as the teeth are de-identified, and not trackable to their owners.[46] The MIU IRB standardized the handling of freshly extracted unidentified teeth at MIU clinics and of teeth collected outside the university, according to the US Centers for Disease Control and Prevention guidelines.[36]

Pharmacy Protocols

Chemical Synthesis and Analysis of Preexisting Material

Pharmacy protocols reviewed by the IRB were either the synthesis of new biologically active chemical moieties or the analysis of preexisting pharmaceutical compounds. The common ethical concerns regarding these protocols were the type of biological material, whether the biological samples were identifiable, method for obtaining these samples, and presence of material transfer agreements and Egyptian authorities' approval for the transfer of these biological samples from the campus to any other institution in Egypt or abroad.

The extent of the IRB review of synthesis protocols was based on the hazard or risk posed by the study and whether or not the protocol involved human subjects. To perform a "Human Subject Determination" of a protocol, the protocol must include the source of the samples, whether prospectively collected or already existing, and whether they contain identifiers. However, the specimens used in all pharmacy protocols were received from commercial biobanks and repositories and were all de-identified. Hence, the studies were all determined to be nonhuman subject protocols, not involving human subjects, and with no risk to the investigators when standard safety precautions were followed.

Study limitations

The current review has limitations as it was conducted retrospectively to analyze the protocols. The meeting minutes might not have properly captured all the concerns discussed. Hence, some may have been missed.

Conclusions and recommendations

Numerous dental and pharmacy procedures may pose risks to the patient if proper precautions are not followed. Translating complex terms into Arabic is challenging, but can be overcome by initially writing the informed consent form in Arabic. Experimental gingivitis and the use of new materials in research pose challenges that need to be addressed and reviewed in-depth by the IRB members. Regardless of how minimal the risks are; the IRB should meticulously examine each protocol to make appropriate decisions for the safety of the participants. *In vitro* dental and pharmacy proposals must include sufficient information to enable the IRB to make a proper determination regarding the participation of human subjects. The request for proof of investigators' qualifications should not be underestimated, as it aids in avoiding iatrogenic mishaps and minimizes the risks of the procedures. Research ethics training for IRB members should include practical sessions and workshops using the previously submitted protocols to learn how to identify ethical concerns.

Conflict of interest

The authors of this study have no competing interests that may bias this work.

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Ethical approval

This manuscript was registered on "cinicaltrials.gov" with the identifier NCT05195671.

Author contributions

The first and second authors contributed to the conception and design of this study. All authors contributed to the interpretation of data, drafting, and critical and final revising of the paper.

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