A protocol for developing reporting guidelines for laboratory studies in Endodontology

Abstract

Laboratory-based research studies are the most common form of research endeavour and make up the majority of manuscripts that are submitted for publication in the field of Endodontology. The scientific information derived from laboratory studies can be used to design a wide range of subsequent studies and clinical trials and may have translational potential to benefit clinical practice. Unfortunately, the majority of laboratory-based articles submitted for publication fail the peer-review step, because unacceptable flaws or substantial limitations are identified. Even when apparently well-conducted laboratory-based articles are peer-reviewed, they can often require substantial corrections prior to publication. It is apparent that some authors and reviewers may lack the training and experience to have developed a systematic approach to evaluate the quality of laboratory studies. Occasionally, even accepted manuscripts contain limitations that may compromise interpretation of data. To help authors avoid manuscript rejection and correction pitfalls, and to aid editors/reviewers to evaluate manuscripts systematically, the purpose of this project is to establish and publish quality guidelines for authors to report laboratory studies in the field of Endodontology so that the highest standards are achieved. The new guidelines will be named– "Preferred Reporting Items for Laboratory studies in Endodontology" (PRILE). A steering committee was assembled by the project leads to develop the guidelines through a five-phase consensus process. The committee will identify new items as well as review and adapt items from existing guidelines. The items forming the draft guidelines will be reviewed and refined by a PRILE Delphi Group (PDG). The items will be evaluated by the PDG on a nine point-Likert scale for relevance and inclusion. The agreed items will then be discussed by a PRILE Face-to-Face consensus meeting group (PFCMG) formed by 20 individuals to further refine the guidelines. This will be subject to final approval by the steering committee. The approved PRILE guidelines will be disseminated through publication in relevant journals, presented at congresses/meetings and be freely available on a dedicated website. Feedback and comments will be solicited from researchers, editors

and peer reviewers, who are invited to contact the steering committee with comments to help them update the guidelines periodically.

Keywords: laboratory studies, Protocol, reporting guidelines, quality, Endodontics, Endodontology

Introduction

Research in the field of Endodontology provides new knowledge and can drive innovation and technology, which in turn can help practitioners deliver improved patient care. The ultimate goals of research in Endodontology are to save teeth, alleviate pain, and to restore or replace oral tissues to improve the oral health of individuals and populations. Such research can follow several pathways and stages such as: Basic (experimental), Clinical and Epidemiological (Röhrig *et al*. 2009). The two leading endodontic journals (International Endodontic Journal and Journal of Endodontics) include a section of Basic Research that consists of two subsections: biological and technical. In order to conceptualize reporting guidelines, it is important to understand the definition of what constitutes basic research: 1. It is an experimental or theoretical piece of scholarly work that aims to acquire new knowledge and observable facts. 2. On some occasions, there is no particular application that flows from the work and it may not give a complete specific answer to any specific problem or question (Rubio *et al*. 2010, Tijssen 2010).

The journal Science has published two editorials by Dr Francis Collins, the NIH Director addressing the importance of basic research for the development of Medicine and other specialties (Collins 2012, Collins *et al.* 2016). Dr Collins reported that most of the significant medical advances could be tracked to basic research that had no explicit link to disease, and that basic research funded by the NIH accounted for more than 135 Nobel prizes (Collins 2012). Similar to Medicine, the use of basic research, as well as animal and clinical research, underpins our knowledge of Endodontology.

Endodontic journals publish manuscripts in a wide range of research areas and with an extensive array of study designs. It has been reported that laboratory studies, a form of basic research, makes-up the majority of articles that appear in the two leading Endodontic journals surpassing by far the amount of clinical research (Krithikadatta *et al*. 2014). Unfortunately, a large proportion of laboratory studies that are submitted for publication are not accepted, with evidence that more than 85% of manuscripts submitted to one endodontic journal are rejected (Ahmad *et al*. 2019). The three most common reasons that scientific studies are rejected includes i) the manuscript lacks originality and it repeats information that is already known; or ii) the manuscript failed to conform to author

guidelines, ethical guidelines, and/or the standard of English was too poor to allow it to be published, or iii) the contents of the manuscript are novel and original, but it contains serious experimental flaws that make the results and conclusions biased, distorted or unreliable, with little contribution to current/existing knowledge. To help authors avoid manuscript rejection and correction pitfalls, which can prevent them from publishing their research, and to prevent the wastage of their time, money and careers working on non-publishable investigations that are rejected by high-quality peer-reviewed journals, there is a clear need for professional guidance standards in addition to institutional mentorship and support.

Laboratory-based research in Endodontology include the so-called "*in vitro*" and "*ex vivo"* studies. In Latin, *in vitro* means "within glass", and this term is most properly confined to laboratory studies that are actually conducted using test tubes or other similar glass/plastic vessels. In Latin, *ex vivo* means "out of the living" and this term should refer to describe laboratory experimentation or measurements done in or on tissue explants or fluids collected from an organism, e.g. extracted teeth, biopsied tissues, plaque, saliva, blood. In addition, "laboratory" studies can mean any study not done in the clinic, often involving physical testing equipment and high-power microscopes. For example, laboratory "bench-top" studies can investigate instrument fatigue-resistance, shaping, cutting, centring ability of instruments in simulated root canals, investigate the microtensile bond strength of materials and sealers, and many other types of mechanical testing. This extensive range of studies use a substantial variety of analytical tools and are different from clinical research that includes trials with human subjects to test safety, effectiveness, observational studies, outcomes and epidemiological research (Röhrig *et al*. 2009).

One of the main advantages of laboratory-based studies is that they can be carried out using well-controlled experimental conditions, which can allow the precise effects of independent variables on dependent variables to be measured and compared for differences between individual treatment groups. This is of utmost importance, because there are certain conditions that cannot be standardized adequately in clinical studies for technical or ethical reasons. This helps to determine the cause and effect relationship between these variables. Additionally, in laboratory studies unwanted variables (sometimes known as artefacts) can be isolated or controlled. To meet the goal of advancing knowledge founded

on accurate and reliable research, it is essential that scientific studies are performed in such a high-quality manner, that they can be replicated and duplicated by following the steps described within the materials and method section (White 1995, Faggion 2012, Krithikadatta *et al*. 2014).

Major discrepancies can exist between the results obtained from laboratory studies and clinical outcomes (Van Meerbeek *et al.* 2010, De-Deus 2012). For example, an interesting pathway can be observed in the publication of dye leakage studies. Pitt Ford (1983) recognized the lack of correlation between the seal of a root filling in the canal and the tissue response in an animal study. Wu & Wesselink (1993) reported that in 1990, there was one leakage study to every 4.3 scientific articles within Endodontology. Subsequent clinical data from Oliver & Abbott (2001) revealed that the periapical status of root filled teeth could not be predicted from the results of dye leakage studies. The same was true for studies evaluating the antibacterial effects of endodontic substances and materials by the agar diffusion test (ADT). Because the conditions of the test do not reflect those of intracanal use and the inhibitory effects of a substance depend on its solubility, diffusion through and interaction with the culture medium, the results from the ADT could not be reliably interpreted. For instance, there are ADT studies reporting no antibacterial effects for calcium hydroxide (DiFiore *et al.* 1983, Siqueira & de Uzeda 1997).

In 2007, the Journal of Endodontics published an editorial limiting the number of submissions associated to dye leakage and agar diffusion studies (Editorial Board of the Journal of Endodontics 2007). Not long afterwards, the International Endodontic Journal published a series of editorials on the theme "Research that Matters" in an attempt to inform potential authors of the areas and experimental techniques within specific topics within Endodontology that were either acceptable or not acceptable for consideration for publication (https://onlinelibrary.wiley.com/page/journal/13652591/homepage/research_that_matters_collection.htm).

It appears that the majority of laboratory studies undertaken and submitted for publication in Endodontology are the work of undergraduate or postgraduate students as part of their curriculum. Clearly, the time students can devote to a research project is limited and this tends to be reflected in the fact that most undertake small laboratory-based experiments, which are easier to design and complete within the time frame of a training programme. As a consequence, the scope, depth and impact of these studies is usually limited and to a large degree depends on the funding and facilities available to students, the research culture and environment at their institution and the number and availability of experienced supervisors.

As previously explained, basic laboratory research studies cannot yield information on clinical efficacy. This is the reason why the data obtained from laboratory studies needs to be further evaluated in animal studies and clinical trials, or alternatively be shown to be equivalent to existing materials or instruments to avoid extensive testing, according to the International Organisation for Standardization, outlined within standards ISO 10993 and ISO 7405, before the novel instruments or novel materials can safely be sold commercially for use on patients.

Faggion (2012) used a Modified CONSORT checklist with 14 items for reporting *in vitro* studies on dental materials. A new guideline has also been proposed to develop a Checklist for Reporting *In vitro* Study (CRIS) for dentistry (Krithikadatta *et al*. 2014). However, to help improve the quality and reproducibility of their laboratory-based investigations there is a need for scientific publishing guidelines for researchers in the field of Endodontology. The purpose of this paper is to set out the process that will be adopted to develop guidelines for authors to use when reporting laboratory studies in the field of Endodontology, the Preferred Reporting Items for Laboratory studies in Endodontology (PRILE). The PRILE guidelines will consist of a checklist and a flow chart. The checklist will contain the essential items that should be reported in a laboratory study whilst the flowchart will provide concise information on the sequential steps involved in performing a high-quality reproducible investigation. The modified CONSORT checklist for *in vitro* studies of dental materials (Faggion 2012) will be used as a template to cover the essential components for reporting laboratory studies in Endodontology. In addition to the modified CONSORT

checklist, in the new PRILE guidelines, several additional items will be included, such as: advice on the title, the list of keywords, details of institutional ethics, loss of sample during experiments, strengths and weaknesses of the study, future implications and conclusions.

Due to the variability and inconsistency in the quality of images reported in the literature, Lang *et al*. (2012) developed the Clinical and Laboratory Images in Publications (CLIP) principles. The CLIP principles aim to increase the accuracy, validity and credibility of images in publications. Inclusion of a section on the quality of images in the PRILE guidelines will prevent misleading reporting and reduce missing information that may have a negative impact on the accuracy of interpretation and implications of images (Lang *et al.* 2012). The PRILE guidelines will be important for authors to effectively plan and design laboratory studies and then develop high quality manuscripts in Endodontics in order to benefit scientists, clinicians, and patients. The guidelines will also guide reviewers and editors of journals when they evaluate manuscripts submitted on laboratory studies.

Methods

The development of the PRILE guidelines will employ a similar methodology to that used to develop the Preferred Reporting Items for Case reports in Endodontics (PRICE) guidelines (Nagendrababu *et al*. 2018) and the Preferred Reporting Items for RAndomized Trials in Endodontics (PRIRATE) guidelines (Nagendrababu *et al*. 2019) and will comply with recommendations from the Guidance for Developers of Health Research Reporting Guidelines (Moher *et al*. 2010).

Phase I: Initial steps (developing the concept and setting up a steering committee)

Following a thorough literature search, the project leaders (VN, PD) confirmed that no widely used specific guidelines existed for reporting laboratory studies in Endodontology. A steering committee made up of the project leads (VN, PD) and eight other members (PM, RO, OP, IR, JS, EP, JJ, SP) will create draft PRILE guidelines (checklist and flowchart) based on the modified CONSORT checklist of items for reporting *in vitro* studies of dental materials (Faggion 2012) and the Clinical and Laboratory Images in Publications (CLIP) principles

(Lang *et al*. 2012). The steering committee will be responsible for executing the subsequent phases of the guideline development process.

Phase II: Pre-meeting activities

An international group of experts, the PRILE Delphi Group (PDG) will be formed. The PDG will include 30 members including 22 academicians or researchers and four Endodontists, who must satisfy at least one of the following criteria to be eligible to participate in the Delphi process: 1) published at least two laboratory studies in Endodontics; 2) published any reporting guidelines for research; 3) a minimum of 15 years clinical experience in dentistry. Additionally, two general dentists and two public representatives will be invited to be part of the PDG. The PDG will engage in a structured Delphi consensus exercise to refine the draft guidelines using an iterative online process. An information pack will be prepared and shared with the PDG members that will explain the Delphi process and highlight their role in building the consensus on the inclusion or exclusion of the proposed items in the draft PRILE guidelines.

PDG members will feedback their opinions on the clarity and suitability of each item of the draft PRILE guidelines using a dichotomous scale (yes or no) and a 9-point Likert scale (1-definitely not included to 9-definitely included) respectively. To better understand and analyse their responses, the members will be requested to add comments for each item (Maher *et al*. 2015). Items achieving a score between 7 and 9 by at least 70% of PDG members or items with a score of 1-3 by less than 30 % members will be included whereas, items will be excluded from the checklist if they receive a score between 1 and 3 by more than 70% of members or a score of 7 to 9 by less than 30% of members. The items will be revised considering the comments provided by the members and added to the next round of the Delphi exercise. This process will continue until all the items achieve the set inclusion standard and agreement (Agha *et al*. 2017). A summarized result of each Delphi round will be shared with PDG members.

Phase III: Face-to-face consensus meeting

In this phase, the items included in the draft PRILE checklist will undergo a second stage of consensus-building through the work of a second group of 20 experts (18 members and two chairpersons) who will make up the PRILE Face-to-face Consensus Meeting Group (PFCMG). The members of the PFCMG will satisfy the same eligibility criteria as established for the PDG; PDG members will be eligible for the PFCMG. Two students undertaking postgraduate training in Endodontics will be invited to the meeting to express their opinions on the PRILE checklist and flowchart. Following the confirmation of the members, the details of the meeting venue, date and time will be provided to the PFCMG and the postgraduate students. The steering committee will prepare the materials necessary for the meeting, including the agenda, the results of the online Delphi process, the latest draft of the PRILE checklist and flowchart as well as details of the members. These will be shared with the PFCMG at least ten days prior to the meeting. PFCMG members will be appraised of the objectives of the meeting and the project leads (VN, PD) will present the results of the Delphi process. The rationale for including the items in the PRILE checklist and the content of the flowchart will be discussed and there will be opportunities for the PFCMG to further refine the items and the text associated with each. The PFCMG will discuss the development of a document that will elaborate and explain each item in the PRILE checklist and flowchart. Finally, plans for disseminating the guidelines as well as strategies to ensure adherence by authors will be discussed. Notes will be kept of the discussions that occur during the meeting.

Phase IV: Post-meeting activities

The final PRILE guidelines will be agreed by the steering committee after considering the results of the Delphi process and inputs from the PFCMG. An explanation and elaboration document will be prepared by the steering committee that will provide the rationale, evidence and explanation for each item. Additionally, the steering committee will provide at least one example of good reporting for each item. The elaboration and explanation document will be shared with six members (three from the PDG and three from the PFCMG) for their approval. Following this, efforts will be made to publish the PRILE guidelines and supporting documents in peer-reviewed journals and to present them at appropriate conferences and meetings.

Phase V: Post-publication activities

It is anticipated that the use and implementation of the PRILE guidelines will be endorsed by relevant journals. The PRILE guidelines and supporting documentation will be made available on a dedicated website, the Preferred Reporting Items for study Designs in Endodontology (PRIDE) that will be established and made freely available. To expand the reach of the guidelines, efforts will be taken to translate them into various languages. Feedback and criticism on the guidelines will be welcomed and addressed by the steering committee. Additionally, the steering committee will update the PRILE guidelines periodically, to reflect potential changes to good practice.

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