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Concept Note

CRIS Guidelines (Checklist for Reporting *In-vitro* Studies): A concept note on the need for standardized guidelines for improving quality and transparency in reporting *in-vitro* studies in experimental dental research

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Abstract

In vitro studies form a pivotal role in dental research contribution to a substantial evidence base. The reporting standards of these studies are not uniform thus resulting in lacunae in evidence reported. The effort of this concept note is to propose a Checklist for Reporting *in vitro* Studies (CRIS guidelines) that would promote quality and transparency in reporting *in vitro* studies.

Keywords: Reporting guidelines; *in-vitro* studies; quality; transparency

BACKGROUND

Dentistry is a unique field of medicine wherein the combination of a complex oral environment and functionally demanding occlusal loads make it one of the most challenging therapeutic regions to restore. Thus, the twin focus of dental research has been in treating the burden of oral disease and in evolving superior dental biomaterials. Knowledge from dental research is thereby validated through both *in vitro* studies and clinical research.

In vitro studies provide us with the platform to create, compare and check dental materials prior to their clinical application. *In vitro* research is an integral part of clinical decision-making as this helps the clinician to understand the physical, mechanical, and biological properties of dental materials and dental hard/soft tissues. *In vitro* studies thereby forms the major proportion of research that is carried out and published in dentistry. Among the articles submitted in Journal of Conservative Dentistry, 82% are *in vitro* research. A survey of the articles published in few of the leading journals related to dental materials and Endodontics showed that substantial proportion of *in vitro* studies (Dental materials 98%, International Endodontic Journal 88%, Journal of Endodontics 65%, and Operative Dentistry 74%). It is needless to say that the relevance of *in vitro* studies cannot be over-emphasized.

Our understanding of material behavior has been accumulated over the years only through systematic and meticulous *in vitro* research. For example, fracture resistance of natural tooth following endodontic treatment or compressive strength of composite resins cannot be studied clinically. Another reason to rely predominantly on *in vitro* studies is due to the fact that there is rapid advancement in material science and in basic technology used to assess these materials. The time taken to process the *in vitro* conclusions through clinical research is not compatible with the need to ensure temporal relevance. Hence, newer materials are often tested against existing *in vitro* standards and the results are taken to apply to clinical significance. For example, it is known that total-etch technique provides maximum bond strength and newer bonding agents are usually tested against this as standard. Needless to say, *in vitro* studies are easy to perform and are done under controlled environment, thus reducing the risk of bias.

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Nevertheless the acid test is how they translate in the clinical situation.

Results of *in vitro* studies are often applied in research and development of dental material innovations, discovery of new drugs and understanding material behavior. Published *in vitro* studies enable the reader/clinician to analyze and understand the variability affecting the outcome measure of a material, thus facilitating evidence based practice. Systematic reviews of *in vitro* studies can be performed to consolidate evidence about similar materials/technique. This way, manufactures, clinicians and researchers rely on *in vitro* studies to deduce inferences. However lack of uniform methods and reporting hamper the meaningful comparisons of these studies.

CURRENT LACUNA IN REPORTING *IN VITRO* STUDIES

Most of the *in vitro* studies follow an experimental design. In this design, hypothesis testing follows analytical inference between the groups/materials tested. The structure of an *in vitro* study closely resembles that of a clinical trial, in other words, it is a trial conducted in a lab. The merits of *in vitro* studies as compared to that of a trial include: Control over independent variables and unforeseen bias and ease of operation. This improves internal validity of the results. However, one of the major demerits is that it lacks external validity and generalizability to clinical situations. Though *in vitro* studies are relatively simpler to perform, they lack certain methodological rigor that clinical trials demonstrate.

Existing lacunae among *in vitro* studies that need to be addressed to promote quality and transparency of evidence could include the reporting of:

Sample size calculation

The significance of sample size is well-understood and needless to say it has a huge impact on the results of the study. One of the main reasons for statistically insignificant results could be a small sample size. However, most published *in vitro* studies do not include calculation of sample size as one of the steps in methodology. Instead of choosing the required sample size to test the hypothesis, we tend to choose a statistical method (nonparamentric tests) to analyze data sets from smaller sample sizes. In the place of comparing mean value of the samples and its distribution, we compare median and ranks of median. In situations when we can use actual sample size that allows comparison of mean and the distribution between groups, we are ethically bound to do so. In the event of procuring samples due to cost or feasibility is difficult, a smaller sample size with appropriate statistical method to analyze data could be performed. For example, shear bond strength testing of bonding agents or dentin tubule disinfection studies are methods where required samples size can be assembled without escalating the logistics of the study.

Meaningful difference between groups

One of the information required to compute sample size in estimating mean is the "meaningful difference." Meaningful difference is the difference by which the newer tested material is superior to the existing standard. For example, if the compressive strength of material A is x MPa, then the newer material B should demonstrate a compressive strength of x+x' MPa for it to be superior to material A. Here, x' is the meaningful difference and this measure can only be decided by the researcher. This difference is often set at a measure that would make a difference clinically or scientifically. Meaningful difference is indirectly proportional to sample size. Greater the meaningful difference, lesser is the sample size. However, it is prudent to set this difference as close to clinical scenario as possible. This is a significant step while recommending a new material as a viable alternative to an existing standard.

Sample preparation and handling

A detailed explanation about sample preparation and sample handling helps the reader to understand the simplicity or complexity of the experiment conducted. Information on sample loss at crucial steps would promote transparency of the experiment and minimize bias. For example there is a high risk of sample contamination in a microbiological study. If this risk is calculated before hand and additional number of samples included prior to commencement of the study, then the bias related to loss of sample could be minimized. This is similar to the clinical trial where allowance of 10-15% is made to compensate for drop-outs and loss to follow-up. Another area where sample preparation is important is when we make multiple samples from the same specimen. For example, samples created for micro-tensile bond strength or biofilm analysis on two halves of the same tooth. Technically speaking, these are all samples from a single specimen and cannot be regarded as individual samples. The editor of operative dentistry emphasized in one of the editorials that multiple samples obtained from single tooth for micro-tensile bond testing should be treated as an average for that tooth rather than using individual samples as such.[1] Or, they could be treated as a cluster, and the appropriate correction made in sample size. This is relevant because, if we obtain five samples from each tooth, then three teeth will yield 15 samples. It will be an error to infer from three samples! It would be better to use the five samples from the same tooth to record the variations within the tooth.

Allocation sequence, randomization and blinding

When an experiment is conducted, it is often a single researcher who prepares the samples, allocates them to

groups, conducts the study and assesses the outcome. In the last 5 years there is a change in the method of outcome assessment among many researchers. There are usually two independent observers who assess the outcome of the experiment to promote transparency of the results. However there could be a potential for bias in allocating the samples to the groups. A person independent of the experiment could also do this step. This could be a lab assistant or clerical staff. These methods (allocation concealment and outcome assessment) of blinding can minimize bias. Next is the method of allocating the samples to the groups. Several manuscripts refer to this step as "randomly allocated to groups", however, randomization itself is an important and a systematic step in clinical trials. Randomization refers to the equal and independent possibility of a sample entering any group. The sequence of samples allotted to groups is often predetermined using a randomization chart or a computer generated random sequence table. Randomization:

a Balances known and unknown factors and eliminates bias,
b Permits the use of probability theory that the likelihood of a difference in outcome between groups is by chance, and
c Maintains a certain degree of blinding of samples.[2-4]

Statistical analysis

The statistical method for analyzing data is often a crucial step while rejecting hypothesis in both clinical and in-vitro research. While most authors address analysis for the primary objective, the same for the secondary objective is often not reported. There have also been reports on misuse of statistical methods in dental literature.[5,6] The results of certain studies have completely changed when correct statistics were applied.[7] The editorial published in the International Endodontics Journal provided statistical guidelines for manuscript submissions.[8] It is important to understand that statistical significance is not the deciding factor in a study; rather it gives the researcher a direction towards what the results indicate. Hence to look in the right direction, we need to use the right statistics and apply statistics to both primary and secondary objective if any.

Need for CRIS Guidelines for *in-vitro* dental research

Evidence is categorical in clinical research, whichstates "Assessment of health care interventions can be misleading unless investigators ensure unbiased comparisons. Random allocation to study groups remains the only method that eliminates selection and confounding bias."[9] This has led to formulation of checklists for reporting clinical studies. These include; CONSORT guidelines for clinical trials[9], STROBE guidelines for observational studies[10], STRAD guidelines for studies involving diagnostic tests,[11] and PRISMA guidelines for meta-analysis and systematic review.[12] These guidelines urge the investigator to report the study in concurrence to an itemized checklist. The need for standard reporting of clinical trials first started in the early 1990s and by 1996, the first version of CONSORT was formulated. This underwent modifications in 2001 and 2010.[5] The premise of CONSORT has paved way for other checklists, which are primarily an adaptation of CONSORT to suit their respective needs.[11] The checklist however does not aim to improve the quality of the study but helps to satisfy certain standard requirements that allow comparability across several studies.[9] The success of these guidelines has ensured transparency of clinical studies and has improved evidence based patient care. Systematic reviews and meta-analyses have also become more comprehensive and meaningful. CONSORT guideline has been accepted by over 400 journals since its introduction in 1996. International Committee of Medical Journal Editors (ICMJE) endorses this guideline.[13] There is convincing evidence that journals using CONSORT guideline has improved the quality of reports of clinical trials.[14-16]

Extrapolation of a similar guideline to suit *in vitro* studies would immensely improve the quality of reporting across *in vitro* studies. As of now, there has been no validated guidelines or check list for reporting *in vitro* studies. The prime focus of this concept note is to sensitize the research fraternity regarding this lacuna and propose the concept to develop standardized guidelines for conducting and reporting *in vitro* dental research.

This checklist for *in vitro* studies would be an adaptation the CONSORT guidelines since the methodological structure of *in vitro* study and clinical trial are similar. The checklist would help to address most of the above mentioned lacunae. Apart from this, clear guidelines for reporting would be recommended in the Introduction, Materials and methods, Results and Discussion (IMRAD) format of manuscript preparation. Although items like sample size calculation, meaningful difference, and randomization are not featured in a conventional structure of an *in vitro* study it is obvious that these would make the *in vitro* study reporting robust and significant. In turn the designing of experiments, and their comparability would improve.

A good beginning would be to create a checklist with leads from the CONSORT and to validate the checklist for its effectiveness. A Delphi group needs to be called to identify items in the CONSORT that need to be retained or modified. Focus group discussions and consensus meetings with interested collaborators is mandatory in creating a comprehensive checklist. This checklist then needs to be validated. The J Conserv Dent proposes to undertake the formation and validation of a Checklist for Reporting *In vitro* Study (CRIS guidelines).

CONCLUSION

CRIS guidelines could standardize the reporting of *in vitro* experimental studies in dentistry thereby promoting transparency and quality of these studies.

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