Guidelines for protocol writing

General information:

1-The protocol should be written in "Times new Roman" Font 14, with normal page layout margins, justified paragraph style and line spacing of 1.15. Titles should be written in Bold "Times new Roman" Font 18 and subtitles in Bold "Times new Roman" Font 16.

2-Each section of the protocol (Introduction, Aim, Methods,…) should start in a separate page.

3-The page numbering of the protocol should be at the bottom center of each page.

4-Title page should not be numbered.

5- The candidate should add the page number of each item in the Ethics approval checklist.

6- Words in blue are to be replaced by the relevant data.

Faculty of Dentistry

The British University in Egypt

Title (The population/problem, intervention, control/ comparator, primary outcome , study design & Time factor)

Protocol submitted to
Faculty of Dentistry, The British University in Egypt
for partial fulfillment of the requirements for the Doctor/ Master Degree in
……

By

(Name, Affiliation and degree/s)

Supervised by:

(Main Supervisor Name and Affiliation(s))

(Assistant Supervisor/s Name and Affiliation(s))

Faculty of Dentistry
The British University in Egypt
(year)

I. Administrative information:

1. Title:

Descriptive title identifying the population/problem, intervention, control/comparator, primary outcome & study design.

2. Protocol Registration: (For clinical trials)

Site and registration number of the protocol should be reported before final approval of the protocol (e.g. Clinicaltrials.gov: NCT01066572).

3. Protocol version:

Date and version identifier. (e.g. 25 Jul 2018 Protocol number: 5)

4. Funding:

A description of the sources of financial and non-financial (material) support.

5. Roles and responsibilities:

Names, Email addresses, affiliations, contacts and actual roles of candidate and all supervisors (Coauthors).

Roles: e.g. principle investigator, main supervisor, co-supervisor

Responsibilities: e.g. initiated the study design, will generate random sequence, will provide statistical expertise in clinical trial design.

Name and contact information for trial sponsor.

II. Introduction:(should be to the point and concise)

6. Background and rationale:

Scientific background with all known information related to the point of interest.

7.Statement of the problem:

The research problem should be clearly identified, stating its prevalence whenever applicable.

An understanding of how it is original and relevant.

How the proposed study will help fill the gap of knowledge in the literature.

8.Rationale for conducting the research:

Detailed justification for the trial should be clearly stated including why the research needs to be conducted in the selected population based on the currently available evidence.

Explanation of potential benefits to patients/ health service, relevance to current policies and community priorities.

It is strongly recommended that an up-to-date systematic review of relevant studies be summarized and cited in the protocol.

9.Explanation for choice of comparators:

Selection of control/comparator should be justified with reference including data from an up-to-date systematic review.

Comparator may be:

Placebo, no treatment (Clear reason should be mentioned in case of placebo or no treatment), gold standard, standard of care, another active drug, same drug with a different route or dose of administration.

10.Hypothesis:

A hypothesis states the predicted effect of interventions on trial outcomes.

Avoid biased statements, suggesting the author has prejudged the outcome.

Stated as a Null or alternative hypothesis.

III. Review of literature:

Review briefly the existing body of knowledge on the topic (but not in details).

Description of the current treatment options and their limitations.

Description of the treatment under investigation including; any available data regarding the effects and mechanism of action of the interventions (published and unpublished) and reference to any previous evidence of its usefulness.

Examining benefits and harms for each intervention (summarize the known and potential risks of the intervention, giving a clear description of any expected adverse reactions).

Outline the rationale for the route of administration, dosage, regimen and period selected for the proposed study based on available non-clinical and clinical data.

Explain how the study will substantially add to science, change practice, save money, save lives and/or improve quality of life.

This section should be updated and backed up by a brief and focused literature review of previous related studies highlighting inadequacies in the body of evidence.

IV. Objectives:

Objectives: include aim of the study and hypothesis.

Aim of the study reflects the research questions to be answered by the trial.

Should be clear & very precise, only a few sentences long.

Use neutral words (e.g. “to compare effect of treatment A vs. treatment B on outcome X”) rather than in terms of a particular direction of effect.

Outcome “X” is the primary outcome.

7.PI(E)COTs elements

P: Problem (Population)
I: Intervention. E: Exposure
C: Comparator
O: Outcome (should be measurable and patient related)
T: Time frame. S: Setting

In case of diagnostic test, it will be PIRT (Population, Index test, Reference test and target condition)

8.Research question:

Research question should be clear, properly formulated and well-structured followed with a question mark at the end (PICO format).

V. Methods

9.Trial design:

Description of trial design, including the type of trial (e.g. parallel group, cross over etc.) and allocation ratio & framework should be included.

Framework of a trial is objective to test superiority, non-inferiority, or equivalence of one intervention with another.

The most common design for RCTs is parallel group, two arm, superiority trial with 1:1 allocation ratio.

A- Participants, interventions & outcomes

10. Sample size calculation

Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations. This should include:

1. The primary outcome.
2. Values for outcome (mean & SD).
3. Statistical test used for calculation.
4. Alpha level of significance (5%)
5. Power (80%)
6. The calculated sample size.
7. 20 -30% increase for anticipated missing data depending on nature of study.
8. A reference for outcome assumed.

Example: To compare clinical and radiographic criteria of deep carious lesions after partial removal of caries vs stepwise excavation in the form of pulp vitality, independent chi square test

will be done. A total sample size of 102 will be needed (51 in each group), if the true success rates were 0.69 and 0.91 in SW and PCR respectively based on previous study by Maltz et al., 2012[10], with a power of 80% and 5% significance level. This number have to be increased to 132 to compensate for losses during follow up by 30%. Sample size was calculated by PS (power and sample size program)[11].

11. Study settings:

Description of the environment in which a trial will be conducted (e.g, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained. (Unicentred/ Multicentered)

***In case of vitro studies: mention places of;**

Specimen's collection, processing and examination. Also devices used in specimens examination should be specified

12. Eligibility criteria (For clinical trials)

Eligibility criteria for potential trial participants i.e. Inclusion and exclusion criteria for participants.

They can relate to demographic information; type or severity of the health condition; previous or current treatment; diagnostic procedures; pregnancy; or other relevant considerations.

In trials of operator-dependent interventions such as surgery, it is usually important to promote consistency of intervention delivery by also defining the eligibility criteria for care providers and centers where the intervention will be administered.

Try to avoid restrictive participant selection. When trial participants differ substantially from the overall population to whom the intervention will be applied, the trial results may not reflect the impact in real world practice settings thus affecting the external validity (generalizability or applicability)

- **Patient informed consent if applicable should be attached** (Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable).

13. Recruitment:

Strategies for achieving adequate participant enrolment to reach target sample size.

1. Where?
2. By whom?
3. When?
4. How?

5. Expected recruitment rates.
6. Duration of recruitment period.
7. Financial/non-financial incentives to investigators/participants.

B- Assignment of interventions

14. Allocation:

14a. Randomization:

Key elements of Random Sequence Generation in protocol are:

1-Method of random sequence generation (computerized random number generator).

2- Allocation ratio (1:1, 2:1).

3- Type of randomization: simple, blocked, stratified.

14b. Allocation concealment mechanism:

Mechanism of implementing the allocation sequence (e.g. central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.

14c. Implementation

Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions?

15. Masking/blinding:

Who will be blinded after assignment to interventions (e.g., trial participants, investigator/surgeon, outcome assessors, data analysts, statistician…) and how.

16. Interventions

-Description of Intervention/Control, including how and when it will be administered, with sufficient detail to allow replication.

For drugs, biological agents, or placebos, the protocol description should include:

- Generic name, manufacturer, constituent components, route of administration & dosing schedule.
- The description of non-drug interventions—such as devices, surgical procedures needs additional details about the settings and individuals administering the interventions. e.g., the level of individuals administering these interventions (e.g, for surgeons).

- When intervention delivery is subject to variation, it is important to state whether the same individuals will deliver the trial interventions in all study groups, or whether different individuals will manage each study group.
- Interventions that consist of "standard of care" require further elaboration in the protocol, as this care can vary substantially across centers and patients.

In case of RCT;

-Strategies used to improve adherence to intervention protocols, and procedures used to monitor these strategies (e.g. Pill count, adherence reminder sessions).
-Relevant care/interventions that will be permitted or prohibited during the trial.
-Criteria for discontinuing allocated interventions for a participant, if applicable, e.g. allergic reactions have been observed in rare cases. If this is suspected withdraw the trial medication from the patient.

17. Outcomes:

Primary, secondary and other outcomes should be described, with specific and measurable assessment unit.
It is important to explain the rationale for the choice of trial outcomes.
An ideal outcome is:

1. Valid reproducible
2. Relevant to the target population.
3. Responsive to changes in the health condition being studied.

Primary outcome should be:

- Defined in the PICO.
- Of greatest therapeutic importance.
- Essential for decision-making.
- Used in sample size calculation (mostly)
- Preferred to be patient oriented or patient-centred or patient-reported.

Prioritization of Outcome	**Outcome**	**Method of Measurement**	**Unit of Measurement**
Primary outcome	Pain	Visual analogue scale	Numerical

C) Data collection, management, and analysis:

18. Data collection methods

Plans for assessment and collection of outcome, baseline and other trial data, including processes used to promote data quality (e.g. duplicate measurements, calibration of assessors)

Description of study instruments used for data collection, along with their reliability and validity.

Describe clearly the data collection process:

1. The personnel (standardized training=consistency).
2. Methods (standardized methods variability).
3. Data collection instruments, valid & reliable (questionnaire).
4. Data collection forms (appendices/reference).

Plans for data collected from participants who discontinue or deviate from intervention protocols

19. Data management:

Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry). Reference to where details of data management procedures can be found should be included.

D) Data monitoring:

20. Monitoring (RCT)

Formal data monitoring committee

21. Harms (RCT)

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct.

22. Audit

Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor.

Ethics and dissemination

23. Research ethics approval

Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

24. Confidentiality

How personal information about enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial.

25. Declaration of interest

Financial and other competing interests for principal investigators for the overall trial and each study site

26. Access to data

Statement of who will have access to the final trial dataset.

27. Post-trial care

Provisions, if any, for post-trial care, and for compensation to those who suffer harm from trial participation

28. Dissemination policy

-Plans for investigators to communicate trial results to participants, healthcare professionals, the public, groups (e.g., via publication), including any publication restrictions.

-Authorship eligibility guidelines and any intended use of professional writers

-Plans, if any, for granting public access to the full protocol & participant dataset.

VI. Appendices

29. Informed consent (RCT)

Model consent form and other related documentation given to participants.

30. Biological specimens (Biological specimen)

Plans for collection, laboratory evaluation, storage and getting rid of biological specimens for genetic, histopathological, or molecular analysis in the current trial and for future use in ancillary studies, if applicable.

31. Checklist for the Ethics approval

Attach the checklist and mention the page number in each part.

VII. References

All references should be written in the same font, and should be written through a citation/reference manager e.g. Mendeley or endnote. All references should follow the same style .

الملخص العربى للبحث (مختصر)

صفحة العنوان و المشرفين

- **مقدمة مختصرة**
- **اهداف البحث**
- **طرق و اساليب البحث**