Editorial

Conducting Evidence-based Research: Interventions and Observational Analytic Studies.

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Introduction:

The basic difference between conventional research and evidence-based research (EBR) is that EBR relies on the use of prior research in a systematic and transparent way to inform a new study so that research questions can be answered in a valid and efficient manner and published in an accessible medium[1-2]. A new study should only be informed by systematically examining existing evidence to determine the need of such a study, design, and methods. Knowing how to conduct evidence-based research is a necessary skill for practicing optometrists, academic optometrists and other health professionals. Evidence-based research is an offshoot of evidence-based medicine, which seeks to use the best available research evidence, coupled with the clinician's experience and patient values to provide the best possible quality care. In conducting EBR, each researcher should follow professional, ethical and legal norms. The essential value of EBR is to avoid research waste and to provide answers to practical clinical and Public Health problems. This paper presents the essential elements of evidence-based research, the design and conduct of intervention and analytic observational studies.

There are different reasons why people conduct research. For students in academic institutions, researches are conducted largely as part of the requirement for the award of a degree. For academicians, most studies are conducted simply because they are expected to publish for promotion, or they would perish". In order to avoid perishing, many conduct researches and publish in journals with little or no impact factor. For the above reasons, there has been a proliferation of journals many of them unable live up to their first anniversary.

In many of these scenarios, research resources (funds, materials) and effort are wasted. In healthcare, numerous examples abound of research waste which arise from questions irrelevant to public health, clinicians and patients, inappropriate design and methods, inaccessible publication, and biased and unusable reports. For example, it has been reported that majority of the clinical trials conducted in the later part of the twentieth century and published in major medical journals were not evidence-based, i.e did not present any systematic reviews of existing evidence to justify the need for the research [3-5]. Many were designed without specification of the primary outcomes. Others were conducted with design flaws. EBR aims at addressing these shortcomings. In industry and many organizations, research is conducted primarily for the purpose of breaking new frontiers such as, new technological advancement, new and effective drugs, new and effective intervention programmes.

Difference between Basic and Applied Research

Basic research is a scientific investigation conducted without any conscious goals (of further application) apart from the desire to unravel the secrets of natural phenomenon. For example, an investigator may want to answer a research question "How many legs does a centipede possess? What are the power profiles of commercially available contact lenses? The results from such investigations do not have direct immediate practical application but merely adds to the already existing organized body of scientific knowledge. Applied research on the other hand are conducted with the goal of exploiting the findings to the point at which they can be applied to meet a specific need in an industry or organization. Evidence-based research is intuitively, applied research because the evidence is intended to lead to better patient care, newer more efficient Public Health programmes and better approaches to diagnosis. Evidence-based research is an off-shoot of Evidence-based medicine (EBM) pioneered by a Scottish physician, Archie Cochrane. EBM involves the use of best research evidence for deciding on the best possible quality of care rather than relying on expert opinion, case reports and tradition.

Evidence-based research (EBR) is "the use of prior research in a systematic and transparent way to inform a new study so that it is answering questions that matter in a valid, efficient and accessible manner". So EBR differs from other researches in the sense that before even a topic is selected, there has to be an extensive accumulation of evidence that a knowledge gap exists. Thus, deciding on the conduct of EBR is informed primarily by a detailed and extensive systematic review of evidence. Evidence refers to what is proved by studies conducted according to the best research methodology. Our discussion on the conduct of EBR does not claim that the steps are mutually exclusive nor that the steps must follow a particular sequence. Nonetheless, it is always better to have a clearly defined research question before proceeding to other steps.

Selecting a topic and Refining Research Questions on EBR

Before starting any evidence-based research, it is important to define the research question and determine if any systematic review has already been conducted on this question. A systematic review is a summary of primary studies aimed at addressing a specific problem based on a pre-specified criterion. The steps in conducting a systematic review include defining the review question, planning the eligibility criteria, planning the search methods, actual search for the studies, applying the criteria, collecting and extracting data, appraising the studies for risk of bias, analysing and presenting results, interpreting the results and drawing conclusions. A systematic documentation (e.g. registration with PROSPERO, Cochrane Collaboration or Campbell Collaboration) of the review plan is what makes a systematic review different from the traditional literature review. Acquiring evidence for refining an EBR topic and for searching relevant literature can be a difficult task. A systematic review can even be a stand-alone project by itself.

The first step is to write a focused clinical or public health question. Evidence-based Research may focus on an Intervention, Diagnosis, Risk factors/Aetiology, or Prognosis. Although formulation of appropriate research questions may be a difficult task, it can be made easier by using a **PICO** approach to break down the research question into smaller parts and identifying key words that would be useful during our systematic reviews.

In considering **P**, we are to ask questions such as : What are the characteristics of the **p**opulation we are interested in? Who are the relevant **p**atients/subjects? We want to be specific with respect to age, sex, geographic location, or specific characteristics that would be important to our enquiry. The **P** can also represent the Problem; the disease condition, that one is interested in.

We represent **Intervention** which in the case of optometry and Public Health may range from simple to complex. We wish to answer the questions: What Interventions are we interested in? Do we plan to treat, diagnose, provide service (customized glasses), prevent or observe?

C stand for Comparison: What is the **comparison** or alternative to the intervention? Is it a different drug, placebo, surgery, etc.

O What are the outcomes of interest? These must be specified ahead of the systematic review and before our new study. Interestingly, many of the randomized clinical trials conducted in the 1990s, especially those funded by pharmaceutical industries were done without specifications of primary outcomes in advance. Because the particular outcomes were not specified, it was common place for investigators to search for as many outcomes as possible. Of course, the more parameters are investigated, the more likely differences would be found between the test drug and the placebo by chance; even differences in outcomes that may not be related to the key issues of effectiveness and safety.

An example of a **PICO** question for EBR may be: Does full time patching (I) in adults with amblyopia (P) lead to a regain of visual function (O) compared to those without patching? We might put it in another way: Are adults with amblyopia (P) more likely to regain visual function (O) following full time patching (I) compared with those without (C)? In a risk factor evaluation, we might also ask: Is there an association between cigarette smoking (I) and the occurrence of macular degeneration (O) among adult Nigerians(P)?

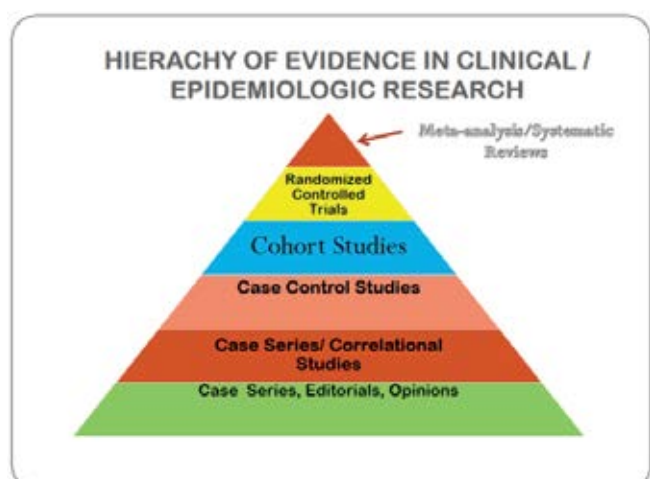## Conducting a critical Appraisal of the Literature:

To provide any valid evidence, a single study must truly measure what it purports to measure. The following questions may be asked to appraise the validity of research:

1. What is the research question, are the objectives of the study clearly stated and why was this research necessary?
2. Is the research original or important? Does the study have new findings? Is a treatment outcome clinically relevant?
3. Does the research question consider the following?

- The group or population of patients
- The intervention or therapy
- The outcome

4. Did the authors use appropriate study design for the research question?
5. Did the study design minimise the risk of bias in its methodology, reporting, and patient selection?
6. Was the study designed in line with the original protocol? Is the focus of the report in keeping with the study objectives? Were changes made to the inclusion or exclusion criteria?
7. Has the study's hypothesis been tested?
8. Is the analysis of the data accurate? What level of uncertainty surrounds any results?
9. Are the conclusions based on the data and analysis? Do the authors draw conclusions that are supported by the data? Have the authors discussed other work that both supports and contradicts their findings? Have the authors identified any limitations to their study?
10. Does the study contribute to the understanding of the problem being investigated? What are the strengths and limitations of the study? Are the findings of the study useful for clinical practice? Do the risks of a treatment or diagnostic procedure outweigh the potential benefits?

Levels of evidence:

The weight or level of evidence ascribed to a primary study when making decisions about clinical /public health interventions depends on the study design and are presented as follows in descending order.

HIERACHY OF EVIDENCE IN CLINICAL / EPIDEMIOLOGIC RESEARCH

Meta-analysis/Systematic Reviews

Randomized Controlled Trials

Cohort Studies

Case Control Studies

Case Series/ Correlational Studies

Case Series, Editorials, Opinions

The highest level of evidence is from meta-analysis (a statistical analysis that combines the results of multiple rigorous scientific studies) while the gold standard for an intervention study is randomized controlled trials.

Choice of Study Design:

Now that we have had our research question clearly defined and articulated, our next concern will be on the choice of a study design. Questions that have to do with drug or other medical interventions should be addressed by double blind Randomized Clinical Trials. Questions that relate to prophylaxis (e.g. vaccine trials) should be addressed by Field Trials. Questions on prognosis require longitudinal cohort studies and those about causation or risk factors require either cohort or case-control studies.

This paper is limit to intervention studies and briefly will touch on observational analytic studies and cross-sectional studies.

Intervention Studies:

The most reliable design for evaluating treatments and interventions generally is the randomized controlled trial. The aim of intervention studies is to produce unambiguous evaluations of the effectiveness and efficacy of a new drug, medical or surgical procedure, diagnostic method, educational intervention, etc. Pharmaceutical companies cannot market a new drug or medical device until adequate evidence of its effectiveness is available. Practising and academic optometrist and other health professionals need to have sufficient under-

standing of the process, the design, the conduct and administrative aspects of Randomized Controlled trials. An RCT is a study in which individuals are allocated randomly to receiving a particular intervention or not (this could be two or more different treatments or one treatment and a placebo). There are many design issues that are to be addressed in the design and conduct of an RCT. These include the need for comparable groups in the trial arms, need to minimize bias in subject allocation, the need for objectivity in the assessment of the outcome of interest and above all, the obligation" to do no harm"

Randomization is the process of assigning subjects to the various treatment arms so that the allocation is not influenced by the bias or judgement of the investigator. With randomization, the allocation of subjects to the various treatment groups is by chance, not by choice. Because randomization ensures comparability of the subjects in the different groups, any difference in the outcome of interest can be reliably attributed to the treatment under investigation rather than to other factors. There are varieties in design options of RCT. These include the parallel RCT, Cluster RCT, the Crossover, the Factorial and the Adaptive Designs which are adopted depending on the type of intervention, the study population, and objectives of the study.

Knowing the type of intervention, a patient receives can prejudice the results of a trial. **Blinding** is a process that ensures that neither the subjects or the persons administering the treatments nor the persons assessing outcomes know to whom the various treatments are assigned.

Sample Size considerations in intervention studies

One of the most important considerations in the design of an RCT is the choice of the number of subjects to be included in the study. Study sizes that are too small may fail to detect important effects of the outcomes of interest. Study sizes that are larger than necessary are a waste of resources and often lead to loss of accuracy because it is more difficult to maintain data quality.

There are scientific methods of determining study size. Although these methods have been available for many years, it is probably not an exaggeration to say that the sample sizes in the majority of intervention studies in the immediate past, especially in developing countries were too small. It is an obligation on the part of investigators to determine and use adequate number of subjects necessary to answer the research questions in a valid way. This can be achieved by involving epidemiologists and biostatisticians right from the planning stages of a study.

Ethical considerations in Intervention Studies

Ethical considerations are fundamental to the design and conduct of any research involving human subjects. In many countries, research institutes and universities, research is not allowed unless the protocol has satisfied a formal ethical review committee. In Nigeria, the body that is charged with the responsibility of reviewing and granting such an approval is the National Health Research Ethics Committee (NHREC). The ethical principles that are involved in medical research involving humans are well described in the "Helsinki Declaration, 1975.

Generally, ethical considerations should address the scientific merit, informed consent, confidentiality, potential risks and benefits.

Analysis and reporting of RCTs

The results of an RCT should be reported widely to funding agencies, national health officials and to national and international scientific journals. In order to minimize the potential for misleading interpretations and conclusions, investigators must follow acceptable norms. The most widely acceptable guideline for interpreting and reporting of randomized controlled trials is the CONSORT (Consolidated Standards for Reporting Trials) statement.

Case Control Studies:

A case-control study is one in which a group of individuals who have a particular disease (cases) and those without (controls) are compared with respect to a specific exposure history. Such studies are designed to test hypothesis concerning the association between a suspected causal factor or a risk factor and a disease of interest. For example, in a study of the association between smoking and age-related macular degeneration (AMD), we would compare the history of smoking among individuals with AMD (cases) with those without (controls). Because classic case-control studies were based on the disease conditions which had already occurred, it was sometimes generally referred to as retrospective studies. It should however be noted that a nested design can also be adopted; thus case-control studies and retrospective studies are not exactly synonymous. Diseases for which case-control study design are often used are usually chronic diseases which take a considerable amount of time to develop. It can also be used for acute conditions such as food poisoning, acute diarrhea, conjunctivitis.

Identification and Selection of Cases:

After clearly stating the hypotheses, the first step in a case-control enquiry is to identify the persons who have the disease condition in question (cases). It is important that a set of diagnostic criteria be established ahead of the study so as to avoid the possible effect of misclassification arising from ambiguous disease definition. Cases are generally selected from hospitals, clinics, treatment centres, etc. In population-based case-control studies, cases are selected from the general population. It is a desirable practice to limit the cases to those diagnosed within a given time period.

Selection of Controls:

It is necessary to decide on who would be the control group and from what sources they would be selected. Great care is to be taken in the choice of controls to ensure that they provide a valid standard of comparison with the cases. The basic principle to be observed is that the controls should resemble the cases as closely as possible except for the difference in the absence or presence of the disease. Controls should represent the population from which the cases are selected. Controls can be selected from among patients within medical facility as the cases. They may be peers, friends, family members, neighbours of

the cases. To ensure comparability of cases and control individual and group matching strategies are often adopted.

Sample Size:

As stated earlier in the case of intervention studies, there is an expected minimum number of subjects for every quantitative research. How many cases and controls should be included in my study? This is a very important consideration in the conduct of not just case-control studies, but any evidence-based investigation. For any case-control study, RCT and cohort study, one of the mathematical expressions for the minimum number of subjects in each group[6] is

$$n = \frac{2x\ (Z_\alpha + Z_{(1-\beta)})^2\ X\ p\ x\ (1-p)}{(p_0 - p_1)^2}$$

The explanation of the above expression is shown in the appendix below.

Data Collection on Exposure:

Once the cases and controls have been identified, data are collected on the history of exposure to the specified risk factor. Data are also collected on potential confounding factors. The choice of data collection methods depends on the particular exposure of interest. For personal habits, questionnaires may be used while medical and occupational history can be obtained from secondary sources.

Estimating the association between exposure and the disease condition can be determined by computation of the odds ratio with associated confidence limits while controlling for confounders.

While we use CONSORT as guide for interpreting and reporting RCT, we use STROBE Statement (Strengthening the reporting of Observational Epidemiologic Studies) as a template for guiding the reporting of case-control studies.

Cohort Studies:

A cohort study is one in which a group of individuals

who have a common exposure experience through time (cohort) are followed over time and their health outcomes are compared with individuals without such exposure. In the conduct of cohort studies, the exposure of interest (occupational, environmental, social, or personal characteristics) and how the exposure is to be measured, have to be specified. A comparable group without such an exposure is also followed through time to measure health outcomes. The number of subjects in each group is usually determined using appropriate statistical techniques. The reporting of cohort studies is guided by STROBE just as in case-control studies. The unique advantage of cohort studies is that the incidence (measure of risk) can be determined in both groups and compared to yield relative risk (RR), attributable risk (AR) and population attributable risk (PAR). The major disadvantage is that the duration of study is usually long especially for chronic conditions with long latent periods.

Cross Sectional Studies:

In cross-sectional studies (CCS), information is collected on a well-defined population at a single point of time. With a cross-sectional study design, it is possible to collect information on exposure and disease status simultaneously. Cross-sectional surveys are used to provide information about the prevalence of a disease, or any other health-related state in a defined population. That allows the study to provide an overall snapshot of the characteristics, frequency, or occurrence of the targeted outcome, at any given time, within the population. Because exposure and disease status can be measured simultaneously, it is possible to examine the relationship between them. A major weakness concerning relationships in cross-sectional studies is that a causal relationship may be difficult to establish, particularly with extrinsic factors, since it is often difficult to say which was the "chicken" and which was the "egg". In other words when exposure and disease are measured at the same time, it becomes difficult to establish whether the exposure preceded the disease or vice versa. Because of this serious limitation, cross-sectional studies are usually not classified among classical analytic studies even though hypotheses of association can be tested.

Sample Size for a Cross sectional study

Every research, irrespective of the study design requires

that appropriate sample size, that would be representative of the study population, be calculated. This should usually be considered at the proposal stage of the research. The size of the research sample is dependent on a number of factors such as confidence level, margin of error or level of precision, study population, sampling procedure, study design, non-response rate, power of the study and available resources. There are many formulae for the estimation of sample size for a cross sectional study. See appendix III for two formulae for the determination of sample size for a cross sectional study[7]. After estimating the sample size required for a CCS design, the next important thing to consider is the sampling procedure. We recommend that that sampling procedure that gives every unit in the study population a known likelihood of being selected (Probability sampling techniques) should be considered in a quantitative Cross-sectional study. Non probability sampling procedures are only recommended where probability sampling procedures are not possible.

Conclusion:

Evidence-based research is the use of prior research in a systematic and transparent way to inform a new study so that research questions can be answered in a valid and efficient manner and published in an accessible medium. A new study should only be informed by systematically examining existing evidence to determine the need of such a study, design, and methods. Knowing how to conduct evidence-based research is a necessary skill for practicing optometrists, academic optometrists and other health professionals. Evidence-based research is an offshoot of evidence-based medicine, which seeks to use the best available research evidence, coupled with the clinician's experience and patient values to provide the best possible quality care. In conducting EBR, each researcher should follow professional, ethical and legal norms. The essential value of EBR is to avoid research waste and to provide answers to practical clinical and Public Health problems. For providing evidence of effectiveness of an intervention, randomized controlled trial is the best EBR design option.

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Appendix II: Sample Size for Case Control , Cohort and Intervention studies

$$n = \frac{2x\,(Z_\alpha + Z_{(1-\beta)})^2 \times p \times (1-p)}{(p_0 - p_1)^2}$$

Z_β= Power of the test

Z_α= Z value associated the specified confidence level

p_0= The proportion of the control group with the exposure

p_1= is the proportion of the cases with exposure (estimated from the postulated odds ratio)

$p = (p_0 + p_1)/2$

Appendix III: Sample Size determination for a Cross Sectional Study

Formula one [7]

$$n = \frac{Z\ p\ q}{2} = \frac{Z\ p\ 1-p}{d}$$

Where n is the desired sample size

Z = the apha level of the confidence limit (99% = 2.56, 95% = 1.96, 90% = 1.645)

P = the proportion in the target population estimated to have a particular characteristic of interest (from pervious study)

q = (1-P) the proportion in the target population estimated not to have a particular characteristic of interest.

d = margin of error or precision required eg 3%, 5%. 10%

if p is not known from previous studies, 50% is used

Formula two [7]

$$n = \frac{Z\ (1-P)}{\mathcal{E}^2 P}$$

n = desired sample size

Z = Confidence level at 95% is 1.96

P = Estimated proportion of persons in the population with condition of interest

1 – p =Estimated proportion of persons in the population without condition of interest

£ = Relative Precision is 10% (of 15%)