Basic Understanding of Study Types and Formulating Research Question for a Clinical Trial

Do we know everything about our specialty? Does our literature reflect everything we should know? Does current literature suggest what we should explore in our research considering the lacunae in present evidence? The answer to the first two questions is no while for the last question is definitely yes. Solving each question poses several other questions to solve. Clinical research largely follows step ladder pattern. Understanding lacunae in existing literature requires interest and expertise in the given field as well as thorough review of the relevant literature. It is indeed important to know “where the boundary between current knowledge and ignorance lies”.[1]

Types of Clinical Studies

Clinical research studies are broadly of two types: observational studies and experimental or interventional studies.

Observational Studies

In observational studies, as the name suggests, the observer only observes as such or with tools/relevant investigations and does not interfere with the natural course of the disease/clinical condition. Observational studies are cross-sectional, case control or cohort studies.

Case control studies tell us about association between an exposure and an outcome, while cohort studies assess causality. In case control studies, the outcome of interest has already occurred. Comparing cases (those who already have the outcome of interest) with controls (those who do not have the outcome of interest), researchers look into the past with the aim of finding out the association of exposure and the outcome. In the cohort studies, two groups of individuals, one exposed and one not exposed to a “suspected” exposure causing the outcome, are followed prospectively in time to know whether the exposure actually leads to the outcome. Cohort study may also be performed with a single cohort (i.e. without a control group), where a group of individuals sharing a common characteristic are followed up forward in time to know the outcome of interest.

In a cross-sectional study, study participants are seen only at a point of time and information of interest about them is recorded. Cross-sectional studies are of two types: descriptive and analytical. Descriptive cross-sectional studies are one dimensional and they are done to find prevalence of the disease. They do not attempt to establish association between two parameters in a given disease or condition. On the contrary, analytical cross-sectional studies one tends to assess whether one parameter is associated with the other. However, since time is not a factor in cross-sectional studies, the study being a snapshot in time, the direction of association, that is, one causing the other cannot be established in analytical cross-sectional studies.

Cross-sectional studies are the commonest observational studies performed in dermatological disease and have several advantages. They are easy and quick to perform and economical as study participants are not followed in time. Moreover, several factors can be assessed at a time. The main disadvantage is that a cross-sectional study does not establish causality. Despite this limitation, they are very important as such studies give an idea about associations and pave the way for other observational study types that look into the causality. These studies cannot measure incidence of disease and are not suitable for diseases with low prevalence.

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A majority of the case control studies reported in dermatology are actually analytical cross-sectional studies.

Sometimes good studies have been misclassified as far as the study type is concerned. For example, in studies designated as case control studies, the cases and controls were not traced back in time. Such a study design is an example of analytical cross-sectional study. Similarly, in studies designated as cohort studies, the study participants were not followed up in time. Another common misclassification is “prospective cross-sectional study.” These studies are actually prospectively carried out cross-sectional studies, where research protocol is first framed and then study participants are evaluated at a single point. For a prospective study, a given study participant has to be followed up in time.

**Interventional Studies: Clinical Trials**

Clinical trial is an interventional or experimental study, where the investigator intervenes with treatment or determines the exposure to identify how one treatment arm fares in comparison to the other, the intervention actually changes the progress of the disease. One may also see the effect of one treatment only (single arm trial, which could also be called a prospective cohort study). When the effects of two treatments are compared, one group of patients, called the experimental group, receives the experimental drug, and another group, called the control group, receives the placebo or an active comparator drug.

**Research Question**

As all clinical research endeavors to address a research question, framing the primary research question is of utmost importance as it influences the study design, sample size required and the resources that may be required. All study questions along with the primary research question should be developed at the beginning of the study. Primary research question should never be compromised because the study hypothesis and objectives are framed based on the primary question. Loading a single study with several questions is likely to increase the complexity of the study design and statistical analysis.

Hulley *et al.*[2] suggest the use of FINER criteria for development of good research question. FINER is the acronym for (F)easibility, (I)nteresting, (N)ovel, (E)thical and (R)elevant. Feasibility in terms of availability of adequate number of study subjects within limited study duration is the most important factor to consider in studies conducted in India as majority of the studies form a part of postgraduate thesis. Next important concern is availability of funds and technical expertise as funding for dermatological research is often limited. The study question should be interesting and novel. After all the efforts of conducting a research, it needs to be published for wider dissemination of information gathered. Relevance and correct methodology are most important aspects in a study. However, novelty and interest in the subject are important aspects considered by the reviewing editor for further review. Otherwise, it stands a high chance of getting nixed in the bud irrespective of the strength in the study design. The study should be ethically justified to stand the chance of getting approved by relevant ethics committee. The question should be relevant too. For example, studying keratinocyte or melanocyte tumors in Indian context may not be relevant to clinical practice due to their rare occurrence.

Though FINER criteria determine the overall importance of the study question, the formatting of a research question follows PICOT.[3] It is the acronym of (P)opulation or (P)oint of interest, (I)ntervention, (C)omparison, (O)utcome of interest and (T)ime required for the study that is sufficient to capture the outcome of interest. Defining study population or patients based on inclusion and exclusion criteria is important and it determines validity of the results of the study. Wide inclusion criteria improve the external validity and wider generalizability of the results of the study in clinical practice. Study that does not lead to knowledge generalizable to a larger population is not ethical as it puts study subjects to unnecessary study-related risk with no benefit to anyone. “Intervention” in “PICOT” is only relevant for interventional studies. Other elements in PICOT may be helpful in formulating a study question for observational studies.

The clinical question leads to development of the hypothesis of the study. When formally testing for statistical significance, the research hypothesis should be tested as null hypothesis. Null hypothesis means that there is no difference in outcome between two arms. If there is no significant statistical difference, the null hypothesis cannot be rejected. On the contrary, if there is significant difference, the null hypothesis is rejected in favor of alternative hypothesis which says that one treatment is superior to the other.

Let us try to develop a research question. Literature search suggests that topical corticosteroids remain the gold standard for management of oral erosive lichen planus. Several other drugs including cyclosporine, methotrexate, acitretin and so on have been tried and they are found to be effective. However, evidence for their effectiveness in comparison to topical corticosteroids (gold standard) is not robust.

Let us find whether acitretin is effective in oral lichen planus. Going by the FINER criteria, it should be Feasible (confirmation of diagnosis of oral lichen planus by histopathology, number of patients in given study period, relatively low-cost drugs, clinical assessment of improvement with treatment and treatment outcome), Interesting and Novel (it assesses the place of acitretin in challenging clinical problem in the form of oral lichen planus, no randomized clinical trial of acitretin in this
indication is available and thus novel), Ethical (since acitretin is commonly used in other indications and also in lichen planus, in carefully selected patient population, ethical issue should not be a problem) and Relevant (relevant in day-to-day dermatology practice).

For this study, Population consists of patients with erosive oral lichen planus. However, acitretin must not be used in women of childbearing potential due to its long-term teratogenic effect. Therefore, effective patient population will be adult men or women of non-child bearing age group. This can be taken care in the study methodology (exclusion criteria). Intervention here is oral capsule acitretin 25 mg once a day or dose adjusted as per body weight. The comparator group is topical triamcinolone acetonide oral paste (0.1%). As there is no validated scoring system for oral lichen planus, one can use 90% (arbitrarily chosen) reduction in pain/discomfort using 10-point visual analogue scale as primary outcome measure. One may decide to study a patient over 4 months as this is likely to be sufficient for 90% reduction in pain score as determined from prior clinical experience. This represents time in PICOT format.

A drug which shows efficacy in longer time may not be clinically relevant. Investigator has to decide the time in which the effect of a drug is considered reasonable and clinically relevant. Suppose a drug shows efficacy, but takes a long time to do so, it may be considered clinically irrelevant. It is also likely that those who fail to respond by 4 months may drop out from study if they are continued on same treatment which has been ineffective, and this may be ethically unjustifiable too.

Let us now see what could be the research question and study hypothesis in this scenario. One way of putting the research question would be “Does acitretin 25 mg once a day reduce pain score by 90% in comparison to topical triamcinolone acetonide (0.1%) applied three times a day among adult male patients suffering from erosive oral lichen planus over a 4-month treatment duration?” The Null hypothesis (H0) for this study would be “acitretin 25 mg once a day is as effective as topical triamcinolone acetonide (0.1%) applied three times a day in reducing pain score by 90% in patients of erosive oral lichen planus over a 4-month treatment duration.” Alternative hypothesis (H1) would be that acitretin is more effective than triamcinolone or vice versa.

Once the study question is framed and hypothesis of the study is in place, the best methods to answer the study question by accepting or refuting the study hypothesis are devised. These will be dealt in the subsequent sections.

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Conflicts of interest
There are no conflicts of interest.

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