**Study design in Gastroenterology**

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Basic, clinical, and translational research are an integral part of modern gastroenterology and hepatology. Understanding the importance of study design is critical in early and advanced career stages. Planning new study protocols and writing the study section in grant applications, are just two examples in which proper study design may spell the difference between a successful outcome which advances science (and careers), and the alternative.

**First, let’s ask the right question**

Choosing the correct study design is near impossible if an investigator has not framed their research question in a clear and precise way. For example: “Is compound X good for inflammatory bowel disease (IBD)?” is not a well-defined question, as different interpretations can be assigned to each of its elements. The compound may be given in different doses, and through various routes, a drug can be effective in inducing remission but not necessarily sustaining it, and IBD may refer to different conditions (e.g.- Crohn’s disease (CD) and ulcerative colitis (UC), and even those can be further classified (stricturing vs. penetrating CD; distal UC vs. pancolitis). A useful approach to framing the question could be to use a “PICO” format1, defining the patients, intervention, comparison and outcome. The PICO approach is useful also in non-interventional studies, where intervention is replaced by exposure. In this format, a possible question will be “what is the efficacy of oral drug X at dose Y in inducing remission in patients with mild Crohn’s disease compared to placebo.” Only when the elements of this question are clear, can a study be designed to provide an answer.

**Patients:** Defining a study population is paramount to the study’s integrity and validity. This often involves criteria that are widely used and accepted within the respective field. For example, if one considers performing a study involving patients with irritable bowel syndrome (IBS), using the Rome criteria is logical2. In other conditions, histopathological findings may provide an accurate basis to determine phenotypes. It may be of use to review the relevant literature and acknowledge the instruments and criteria that are routinely used in related articles in the field. Failing to meet the acceptable standards for patient inclusion, may eventually have a detrimental effect on the study’s scientific value and publishability.

**Intervention (Exposure):** Failing to clearly define the intervention or exposure (a wider term, which can also be applied to observational studies) may disrupt the study’s validity in multiple levels. For example, in performing a retrospective chart review looking at the effect of steroid treatment on a disease X, inconsistent inclusion of route (oral or intravenous), type, dose, and duration may result in a non-uniform data collection process, ultimately impairing study validity. Having a clear research question in mind helps to overcome this potential pitfall.

**Comparison:** Comparison is the basis for hypothesis testing. A classic example is an interventional study with treated vs. untreated group. Untreated patients may be completely naive, receive placebo, or treated with the current standard of care (due to ethical or facilitation of enrollment considerations). In general, the comparison group should be drawn from the same underlying population as the case group. Planning the comparison goes hand-in-hand with planning the statistical analysis (which is beyond the scope of this article). Of note, the treatment’s effect size may differ if compared to placebo or to the standard of care, and possibly a larger sample size will be required for the latter.

**Outcomes (and additional variables of interest):** One of the key elements in the PICO approach is determining the study’s outcome – how will success be measured. Outcomes can be a decrease in a disease severity score, degree of inflammation based on endoscopic or histopathological scores, survival, or any other outcome that is relevant to the research question. Not uncommonly, studies have more than one outcome, however defining the primary outcome is often useful, and plays an important role in calculating the required sample size.

Apart from the outcomes, other variables may also be required, especially if a stratified analysis is considered. For example, when conducting a research on “does the use of drug X increase the risk of myocardial infarction compared to the general population”, it might be useful to collect data on body mass index (BMI) and smoking, even though they are not a part of the PICO elements, as these may be important confounders. Consulting a biostatistician or epidemiologist at early stages of project development is useful in planning the data collection process and subsequent analysis.

**Options for study design**

There exist several types of study design each with its advantages and disadvantages, which we cannot cover in detail here. Basically, studies can be interventional or non-interventional, and phenotypes may be known at baseline or develop over time. The most common observational studies are cross-sectional studies, where each subject is evaluated once, cohort studies where disease free individuals are followed over several occasions and examined according to their exposure status, and case-control studies where individuals with disease and an appropriate control group (disease free) are examined for prior exposures. The most commonly utilised intervention study is the randomised controlled trial where we as investigators assign some subjects to an intervention and others to placebo or standard care. Some studies are more appropriate for rare outcomes, some for rare diseases. Some are more prone to certain limitations such as bias and confounding. These factors need to be taken into account when choosing the most appropriate study design <a good basic introduction to this can be found at through the world heath organization (WHO) website : <http://apps.who.int/iris/bitstream/10665/43541/1/9241547073_eng.pdf>, Chapter 3.3

**Feasibility assessment**

Once the question is framed, and a clear data collection and analysis plan and has been prepared, it is time to take a step back, and evaluate whether the plan is ethical and feasible. It is possible that a suggested study design is indeed the best one to answer the question, but the chances of completing it are too small. This is often due to limited resources, sample size, duration, and the rate of event occurrence and study duration. Fellows in training should be alert to such limitations and have a realistic view of projects they take on during the fellowship.

In conclusion, framing a clear research question is key to choosing the right study design. Careful planning, including a clearly defined patient population, intervention (exposure), comparisons and outcomes will help avoid unnecessary pitfalls. Having a predefined data collection and analysis plan in an early stage of the project will facilitate a smoother process, and avoid repeating data collection. Feasibility aspects should be realistically appraised before irreversible commitment of time and resources has been made.

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