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Research primer

Study design: A research primer for low- and middle-income countries

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ABSTRACT

Study design is critical to ensure that research questions are answered in an appropriate and rational manner for all aspects of health, but particularly in emergency care. Appropriate study design selection is one of the most critical decisions to make at the earliest stage of a research project; once this is clear, much of the methodology and sample size estimations should be straightforward. Selection of an appropriate study design is fundamental to good research and deserves careful consideration at the outset of any research project.

The classic gold standard for study design is the double-blind randomised clinical trial, but it is often not possible to achieve this ideal in the busy clinical emergency environment or with the resources available. Descriptive studies are common in emergency care; they include retrospective clinical records reviews, prospective cohort studies and case-control studies. Case reports and surveys can be a useful introduction to research for novice researchers. When sufficient empirical evidence on a topic exists, results of similar studies can be combined in systematic reviews and/or meta-analyses to pool the results from multiple studies to determine stronger evidence for or against an intervention or treatment, but these techniques require specialist expertise and statistical skills.

African relevance

- Study design is critical to ensure that empirical research questions are answered in an appropriate and rational manner irrespective of healthcare system
- Study design is often overlooked during the early stages of planning a research project
- A suitable design is one which addresses the research question raised but considers the clinical setting in which the research will be done

The International Federation for Emergency Medicine global health research primer

This paper forms part 5 of a series of how to papers, commissioned by the International Federation for Emergency Medicine. It describes selecting the appropriate study design based on available study resources and participants in order to answer the research question. We have also included additional tips and pitfalls that are relevant to emergency medicine researchers.

Background

Study design is critical to ensure that empirical research questions are answered in an appropriate and rational manner throughout all healthcare systems, but particularly in emergency care. Selection of an appropriate study design is one of the most critical decisions to make at the earliest stage of a research project. Once the study design is clear, much of the methodology and sample size calculations should follow accordingly.

Pilot studies, are vital in research. Before conducting any study, a pilot study or a preliminary investigation should be considered. Pilot studies, also called feasibility studies, are beneficial in testing recruiting methods, practicality, sample size, and other specifications of each study design. Such studies will prevent changes in protocol and eliminate errors. Remember that it's better to conduct a pilot study, instead of changing the design and failing to conduct the actual study in later stages of research [1].

Perhaps the classic gold standard for study design is the double-blind randomised clinical trial, but it is sometimes not possible to achieve this level of study design in the busy clinical emergency department environment. Variants of the randomised clinical trial design

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are also useful in emergency care research, namely the cluster randomised controlled trial and the stepped wedge design.

Descriptive studies are common in emergency care; they include retrospective clinical records reviews, prospective cohort studies and case-control studies. Case reports and surveys represent the lowest level of clinical research but can be a useful introduction to research for beginners.

Once there is sufficient empirical evidence on a particular topic, the results of similar studies can be combined in the form of a systematic review and/or a meta-analysis to pool the results from multiple studies to give stronger evidence for or against an intervention or treatment. These approaches require specialist expertise and statistical skills and expert advice is required to perform these sophisticated analyses. Selection of an appropriate study design is fundamental to good research and deserves careful consideration at the outset of any research project.

Study design is often overlooked during the early stages of planning a research project. An appropriate design is critical to appropriately answer the research question raised by the investigator. Deciding on an appropriate design is crucial to the success of the study and experienced advice should be sought.

A suitable design is one which addresses the research question raised but considers the clinical setting in which the research will be done, the available resources (both clinical and research) and the availability of potential research participants for that study.

Types of study design

Selection of an appropriate study design is one of the most important decisions made during the early stages of planning a research project. The study design is often obvious from the research question, but there may be more than one appropriate design. Different study designs will have varying feasibilities and different strengths, weaknesses and potential biases. Summaries of the different options are given in Table 1 and Fig. 1.

Any research study should begin with a comprehensive review of the literature, and readers are referred to other articles in this series for further details on how to analyse the literature (Chapter 2). This should identify the gaps in the evidence base that the new proposed study can answer. A formal three- or four-part research question can now be generated, and study designs can be considered.

Randomised controlled trials

The classic gold standard for study design is the double-blind randomised clinical trial (RCT), however, in low resource settings, it is often not possible to reach this level of study design in the busy clinical emergency department environment with limited resources. RCTs are excellent designs to answer questions related to the efficacy of a drug, intervention or other therapeutic method when compared to the existing gold standard. For example, is ibuprofen or paracetamol more effective in the management of pain resulting from ankle sprains? Ideally treatments would be non-identifiable to the participants in the study, and non-identifiable to the investigator. This is referred to as a 'double-blind' trial, and this ideal approach minimises the risks of bias.

Drug treatments can often be blinded by using identical placebo drugs, but other interventional treatments such as dressings or orthopaedic appliances or even surgery cannot be ethically or practically blinded. One method of lessening the bias that results from this lack of blinding is to have an independent third party making the final adjudication on the primary outcome of the study (i.e. a telephone interview about pain score or functional ability, without knowing which treatment which was used), but this approach significantly increases the costs of any trial.

RCTs should ideally be performed in multiple centres and/or multiple countries to ensure generalisability throughout various

Table 1
Direction, strengths, weaknesses, potential biases, utility in emergency care research and level of evidence generated of various study designs.

Design	Direction	Strengths	Weaknesses	Potential biases	Utility in emergency care research	Level of evidence generated
Randomised controlled trial (RCT)	Prospective	Less bias overall; high quality design; minimises differences at baseline; answers single important question.	Answers single important question; costly; difficult to perform, especially in multiple centres; consent difficult in emergency patients.	Selection bias; performance bias; attritionbias; detection bias; reporting bias; measurement bias.	*****	High
Case note reviews	Retrospective	Clinical records readily available; consent generally not required.	Data often not reliable; interrater reliability not reported; lack of data abstractor training; lack of standardised data collection forms; lack of definitions.	Reporting bias; information bias; loss of data bias	***	Low to medium
Database studies	Prospective	Data quality usually high; prospective data collection	Costly and labour intensive	Systematic data bias; inclusion bias; selection bias.	*****	Medium to high
Cohort studies	Prospective	Data quality high; follow up can be planned and high quality.	Expensive; long-term; costly; difficult to perform in the emergency setting	Loss to follow up bias.	**	Medium to high
Case-control studies	Retrospective	Limited	Limited applicability in the emergency setting	Inclusion bias; lack of follow up bias	*	Medium to high
Surveys	Cross-sectional/ prospective	Cheap; usually quick; give almost real-time information	Data quality is low; limited response rates are common	Selection bias; inclusion bias; response bias	***	Low
Sys tematic reviews & meta-analyses	Retrospective	High quality; reliable data; high level of evidence impacts practice	Expensive; time-consuming; needs special skills and training	Minimal	*****	High

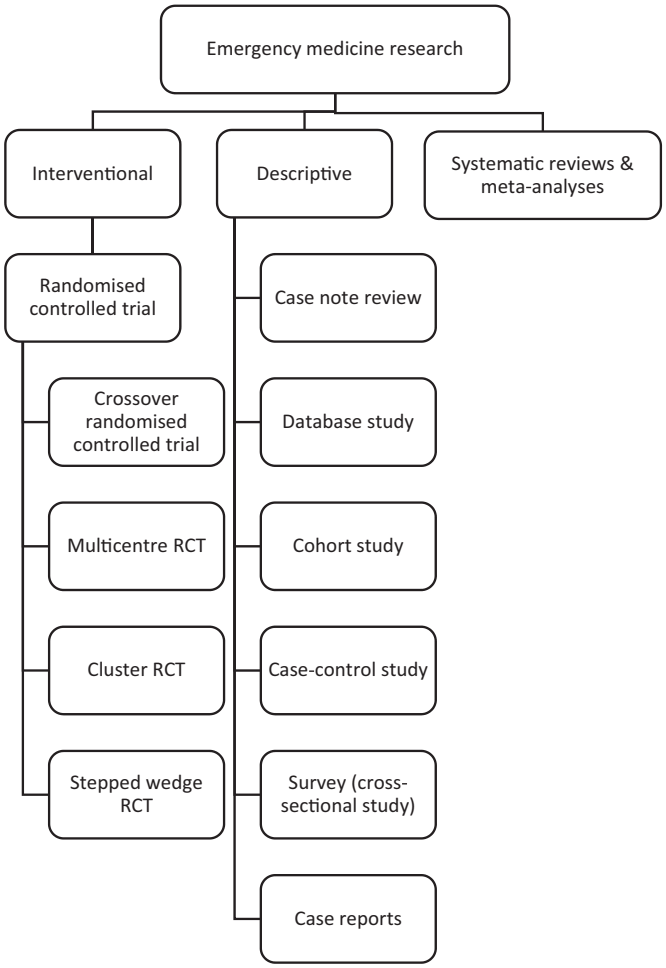

Fig. 1. Study designs.

populations. This increases both costs of and complexity of such a trial. It may be difficult to perform an RCT 24 h a day if research staff are required for recruitment or consent issues; if this is not feasible, it is reasonable to restrict recruitment to office hours only if that approach will still give a valid answer to the research question. This can lead to selection bias, which is a common problem in RCTs. Other potential biases often seen with RCT designs include performance bias, attrition bias, detection bias, reporting bias and measurement bias [2].

Variants of the RCT design can also be useful in emergency care research, namely the cluster randomised controlled trial and the stepped wedge design. In a cluster RCT, instead of patients being the unit of randomisation, a group of patients is chosen as the unit of randomisation. Typically, this would be an emergency department, a hospital, or a group of hospitals, all of which are referred to as 'clusters' in this context. Each cluster is randomised to a particular intervention or treatment and all patients in the trial in that cluster would receive that one treatment.

In a stepped wedge design, instead of all patients in all centres being randomised to one treatment modality at the same time, each research centre is switched over to the intervention of interest at a specific time, so that the effect of time can also be studied. This is also a practical approach for the investigator, as it means that less resources are often required to complete the study.

Another useful variant of the RCT is the crossover trial; patients are given one treatment at the time of initial randomisation, and after a suitable period of time, they are switched to the other treatment under investigation. This approach can lessen the number of participants required for a trial, as each patient effectively acts as their own control. This has the advantage of shortening the time required for the trial and the costs can be lower as well.

All RCTs should be registered prospectively in a recognised study register before the first patient is recruited to the study. Ethical approval is an absolute requirement for all studies regardless of study design.

Descriptive studies

Descriptive studies are common in emergency medicine research. Retrospective reviews of clinical records are perhaps the most common and they can shed light on a specific condition or clinical presentation. The investigator identifies a condition or presentation of interest and retrieves all the case notes of patients who may meet the criteria for the subject of interest. The investigator then reviews all the patient charts and retrieves the information that is required to answer the research question and summarises the data.

While this appears to be a straightforward approach, the reality is very different. Case definitions and data collection forms must be explicitly defined, and each item of data to be collected needs to be clearly spelled out and characterized. Reviewing many case records is time consuming and case records often lack the required information (particularly if clinical notes are handwritten). Interrater reliability for data extraction is often overlooked, but this can be minimised by using two investigators to extract the data alongside standardised data extraction forms and data abstractor training and monitoring [3].

Electronic medical records with clearly defined data fields do make this type of study much more feasible, as long as the required data is included as a field in the electronic record. Retrospective reviews of prospectively collected datasets (e.g. trauma or sepsis databases) are increasingly common and can be of high quality especially if electronic medical records are used as the source of clinical data.

Prospective cohort studies are of higher quality and can generate useful data. Patients with a specific condition or presentation of interest are identified prospectively (i.e. as they present to the emergency department) and data is collected from and about those patients directly, usually by research staff. This greatly increases the quality of the data collected and patients can be followed up throughout their emergency department and/or hospital stay or even beyond that, if they consent to do so. The downside is that they can be more expensive than case reviews because they need research staff support, but they are often much higher quality.

A variant of this type of study are prospective database studies, where data collected prospectively into a clinical database (such as a trauma database) is then used as the source for a descriptive study (see above). The quality of the data is usually higher than a retrospective case note review, but missing data can still be a significant problem. The most common source of bias in cohort studies is loss of follow up bias, as over the duration of the study, it is likely that some patients will be lost to follow up as they change address or phone numbers, or fail to attend their clinic appointments.

Case-control studies are less common in the emergency department setting, but they can be useful to identify possible associations between the condition of interest and any possible epidemiological or causative factors.

Surveys, of patients, relatives or staff, represent the lowest level of clinical research but are a common introduction to medical research for new researchers. The advantage of surveys is that a large amount of information can be collected in a short space of time, from a variety of stakeholders. Challenges include the quality of the information gained; if possible, it is recommended to use a validated tool or questionnaire to collect the data and to be very clear at the outset of the project on definitions for the data that will form the answers to the survey questions. Surveys are particularly prone to biases, including response bias, order of question bias and sampling bias. These can limit the utility of surveys even further.

Case reports are reports of single patients who present with unusual or unique clinical presentations. They are a popular way for new researchers to gain experience in writing and publishing brief papers, but their scientific value is low.

Systematic reviews and meta-analyses

Once there is sufficient empirical evidence on a particular topic, the results of various similar studies can be combined in the form of a systematic review and/or a meta-analysis to pool the results from multiple studies to give stronger evidence for or against an intervention or treatment. Systematic reviews bring together the various papers in an organized systematic manner to ensure that no important studies are omitted. The 'grey literature' should also be searched for these studies; 'grey literature' refers to the unpublished work that is often presented at conferences or is known by the researcher's personal knowledge of the field. Including the grey literature is an attempt to ensure that nothing important is missed out and to minimise bias, particularly publication bias (positive results are far more likely to be published as full papers in the literature compared to negative results). One resource for grey literature can be found at http://www.greynet.org

Meta-analysis is a statistical technique which involves statistically combining the results of similar studies with pooled outcomes to increase the effective sample size for a specific research question. If the pooled sample size is large, then the precision of any estimate of effectiveness will be increased. These research methods require specialist expertise and statistical skills; expert advice and input is required to perform these sophisticated analyses properly.

Qualitative research

Finally, there is an entire field of qualitative research. Qualitative methods include ethnography, focus groups and semi structured interviews. Although relatively uncommon in traditional medical research (and particularly so in emergency care), qualitative research allows an exploration of why events are happening or the barriers and facilitators to changing practice. It focuses on understanding experiences, attitudes, and behaviours. More often, qualitative studies will be combined with quantitative approaches to form mixed-methods studies. They should be considered as a prelude to conducting interventions to help with design and are often a key aspect of evaluations.

Strengths and weaknesses

Each study design has its own strengths and weaknesses as outlined above. Many researchers see the RCT as the design of choice for most studies and there is no doubt that this is an excellent design.

However, in the emergency setting, this is not always feasible for various reasons (availability of research staff; the 24 h/7 day a week nature of emergency care compared to clinic settings; the need for written informed consent in a time critical situation; etc.), so other designs also have valid roles to play in the emergency setting. Cluster RCTs and stepped wedge designs can be useful in situations where individual patient randomisation and consent are difficult or impossible to achieve. The main weaknesses with RCTs are the preparation time involved and the large costs of setting up and managing complex trials.

Descriptive studies (retrospective case note reviews and prospective cohort studies) can be less expensive but are often more time consuming by their nature. Any retrospective design is open to the risk that the information required is simply not recorded in the case records, therefore missing data can be a major challenge.

Surveys are inexpensive and can be done quickly; the level of evidence they generate is low and the usefulness of a survey is often limited. However, if information is needed quickly, they can have merit.

Suitability

Each of these designs is suitable for use in the emergency care setting. Research novices often comment that 'RCTs are too difficult': while there is undoubted truth that RCTs are not easy, they give high quality evidence that allows well-constructed research questions to be answered properly. Some of the biggest questions in the emergency care setting can only be answered properly by an RCT approach, so this should be actively considered wherever appropriate.

Descriptive designs can also be useful, but they are relatively lower quality and they often do not directly answer clinically relevant questions. They are often 'hypothesis generating' studies rather than 'hypothesis answering' studies.

Population and epidemiological studies

Population based or epidemiological studies are also feasible from an emergency care setting perspective, and similar principles should be followed as described above for retrospective case note reviews, case-control studies and prospective cohort studies as appropriate.

Pooling questions across a region, a nation or internationally

It may be appropriate to run a study across a region or country to increase generalisability. Sometimes it is even possible to do a very large RCT across many nations and achieve excellent results which change clinical practice. A good example is the CRASH-2 study [4].

Designing international research often involves collaboration between groups with different levels of experience and resources. Additional challenges of international research design include distance and limited opportunities for face-to-face communication. Specialty conferences can provide additional opportunities to meet if financially feasible. Wireless communication has made international communication faster, easier and less expensive. Language differences and cultural differences must be taken into account by investigators and for the subjects being studied. Make clear who will lead the project, discuss potential bureaucratic obstacles, lay out specific expectations of each author throughout the study and consider consulting an ethicist when developing the study design for cross cultural projects.

Tips on this topic

- Invest the time to get the most appropriate study design to answer your specific research question – don't rush into a study until you have thought the design through
- Get expert help – ideally locally but seek help from the region or the wider emergency care research community to get the best advice
- Review the literature in detail before embarking on a major study – make sure you are not repeating work that has already been done, and ensure that your design is appropriate to answer the question you are asking

Pitfalls to avoid

- Don't feel pressured into doing an RCT to answer every question – there may be good reasons to use an alternative approach in the emergency setting
- Don't avoid doing an RCT if it is the best design for the question – getting a high-quality answer is good for you and for your patients
- Remember to consider the resources you have available for research when planning the design – if you have limited resources (mostly people), then adjust your research approach accordingly.

Brief annotated bibliography

A. Annals EM Paper on case note review standards [3].

- A useful methodological paper on case note reviews

B. CRASH-2 Lancet Paper [4].

- An excellent example of a major international multicentre RCT.

C. CONSORT Website: http://www.consort-statement.org

An evidence-based, minimum set of recommendations for reporting randomised trials. Offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aids their critical appraisal and interpretation. The CONSORT Statement comprises a 25-item checklist and a flow diagram. The checklist items focus on reporting how the trial was designed, analysed, and interpreted.

D. Metholodigical elements for retrospective research studies: https://els-jbs-prod-cdn.literatumonline.com/pb/assets/raw/Health%20Advance/journals/ymem/kaji-1399398337020.pdf

Provides a model that identifies the numerous processes in chart review studies that can introduce bias; (2) to outline the steps an investigator may take when planning a chart review study to mitigate distortion and bias; and (3) to describe reporting techniques that optimize transparency so readers can anticipate the biases and the limitations of the study

E. Guidelines for what to include in Observational Studies using STROBE guidelines: http://strobe-statement.org/

F. Essential Items for Reporting Diagnostic Accuracy Studies using STARD guidelines. http://www.equator-network.org/reporting-guidelines/stard/

G. Guidelines for using Clinical Decision Rules in research:

Clinical decision rules are increasingly prominent in medicine, particularly in emergency care. The quality, use, and impact of current published decision rules widely vary, requiring clinicians to be critical consumers. This is an approach to assist in the appraisal of clinical decision rules and in judging when to use such rules. https://els-jbs-prod-cdn.literatumonline.com/pb/assets/raw/Health%20Advance/journals/ymem/GreenMethodologicStandards-1478702930897.pdf

H. Checklist guide for reporting qualitative research https://academic.oup.com/intqhc/article/19/6/349/1791966

I. Guidelines for Quality Improvement Projects.

The SQUIRE guidelines provide a framework for reporting new knowledge about how to improve healthcare. They are intended for reports that describe system level work to improve the quality, safety, and value of healthcare. http://squire-statement.org/

Authors' contribution

Authors contributed as follow to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content: CAG contributed 65%, JK 25% and ELS 10%. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Declaration of competing interest

The authors declared no conflicts of interest.

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