# Chapter 4.1
## Basic principles in designing studies to assess the effects of interventions

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# Learning objectives

To understand key factors for developing a study to assess the effects of an intervention, action or strategy for health emergency and disaster risk management (Health EDRM), including:

- Importance of reliable and robust estimates of the effects of interventions.
- Minimizing the risk of bias.
- Role of randomized trials.
- Aspects of conducting prospective, comparative studies.

# Introduction

- Decision makers need **reliable and robust evidence** about the likely effects of the interventions, actions or strategies they might implement for individuals or populations.
- To be reliable, this evidence needs to come from studies in which the interventions were compared in ways that minimize the effects of biases and which are applicable to the setting in which the new decisions are needed.
- To be robust, the studies need to be large enough to minimize the effects of chance.

# Randomized trials

- Particular emphasis is placed on **randomized trials**.
- In these **comparative effectiveness studies**, comparison groups differ only in regard to the interventions being compared.
- Some individuals who join the trial are randomly allocated to receive the intervention being tested (often called the "experimental group") and the others are allocated to an alternative or a "control group".
- In cluster trials (chapter 4.3), groups, rather than individuals, are allocated to the interventions.
- The evidence generated shows how the intervention might affect people who are similar to those in the trial, **in the future**.

# Explanatory (or efficacy) trials

- **Explanatory trial:** narrow inclusion criteria to ensure that participants are very similar and will receive/take their allocated interventions.
- Examples: comparing analgesics in people with a specific minor injury or surgical techniques for fractures of the lower leg; or testing a psychological therapy in school children after a tsunami.
- Such a trial determines whether, in these ideal circumstances, there is a difference between the interventions.
- If the experimental intervention is no better than the routine intervention, it is unlikely to be better in a broader population.

# Pragmatic (or effectiveness) trials

- **Pragmatic trial:** In health emergencies and disasters, randomized trials are more likely to include a wide range of participants and less strict control over the specific elements of the interventions being tested.
- Examples: comparing water management methods in camps for internally displaced people or testing antibiotics in people with a wide range of injuries.
- This makes the trial as close as possible to routine practice, with a range of participants  who are representative of those who might be considered for the intervention in the future.

# Uncertainty principle

- **Uncertainty principle**: people might be eligible for a pragmatic trial if there is sufficient uncertainty about the effects of the interventions for them.
- This is a fair way to allocate interventions when a choice has to be made about who is given the intervention, as is often the case in Health EDRM.
- It can be used to decide if a trial is ethical (Chapters 3.4 and 6.4) by considering whether it is ethical to ***not*** do a trial if there is uncertainty about the effects of different interventions which are available and suitable for the population.
- If someone joins a randomised trial, they have a fair chance of receiving the more beneficial intervention (since it is unknown which this is when they join the trial) and the data collected will help to resolve uncertainty in the future.

# Principles of randomization

- Key feature of randomised trials: a random (chance) process determines which of the interventions is received by each participant.
- Differences between the outcomes for those in the randomized groups will be due to the effects of the interventions being compared, or the effects of chance.
- A random sequence needs to be used to allocate participants to their intervention, and no-one should know the allocation before they join the trial, to avoid influencing the decision being made about whether they join.

# Simple randomization

- **Simple randomization**: each participant has the same probability of allocation to each intervention being tested.
- Techniques: flipping a coin, shuffling envelopes into which the allocation has been placed, using random numbers, etc.
- Simple randomization is completely unpredictable if the allocation is concealed until someone enters the trial.
- However, simple randomization can produce chance imbalances in the number of participants or their characteristics between the groups, which might complicate the analysis of the trial.

# Restricted randomisation

- **Blocked randomization:** allows **stratification** of the allocation of the interventions (or a more complex, computer-based technique: **minimization**).
- Blocked randomization means that after a particular number of participants have been allocated, the numbers in each intervention group will be balanced.
- Example: a block size of four in a trial with two interventions guarantees that for every four people joining the trial, two will be allocated to one group and two to the other group.
- Similarly, using blocks for different types of people in the trial (such as young and old people, or those living in rural, semi-urban and urban settings) can ensure balance within those groups.

# Allocation concealment

- **Allocation concealment**: no-one involved in recruiting potential participants knows what they will receive until they have joined the trial.
- Not the same as blinding or masking the intervention.
- Prevents manipulation that might arise if knowing the allocation leads to a different decision about someone's eligibility or their willingness to join the trial.

# Blinding or masking of participants

- Some of those involved in a trial might be "**blinded**" (or "**masked**") so that they don't know which intervention a participant is receiving (e.g. by using a dummy intervention or placebo for the control group).
- Can be difficult and increase the resources needed and make the interpretation of the results more difficult because, in routine practice, people would know what intervention they are being given or taking.
- Trial participants might be kept blind to reduce the risk that they will report outcomes differently because they know which intervention they are receiving or, through a placebo effect, they will respond differently because of this knowledge rather because of the intervention itself; or if knowing their intervention makes them change their behaviour.

# Blinding or masking of others

- Might be important to keep people other than the participant blind to the allocated intervention.
- Keeping practitioners blind ensures that they are less likely to do other things differently for a patient (e.g. adding extra treatments if they know a patient is in the control group or monitoring them more carefully if they are receiving the experimental intervention).
- Keeping people measuring participants' outcomes or collecting data blind means that they don't assess participants differently because of knowledge of their allocated intervention.

# Other types of prospective comparative study

- It's not always feasible to use randomization to allocate the interventions, and other methods might be used.
- Example: for comparing ways to coordinate the response to a disaster, randomly assigning individuals or groups to coordinate their actions in different ways might lead to chaos. Instead, the new method of coordination could be implemented and its impact assessed using a "counterfactual" to estimate what might have happened without it.
- Example: findings from research into a surge of an infectious disease might be used in the evaluation of the impact of a new strategy.

# **Case study:** *Planning an evaluation of strategies that would be implemented in a future health emergency (1)*


- Dengue is the most important infectious disease-related public health concern in Sri Lanka.
- An outbreak at the time of the south-western monsoon rains in 2017 led to approximately 185,000 dengue cases and more than 400 people died.

# **Case study:** *Planning an evaluation of strategies that would be implemented in a future health emergency (2)*


- Researchers at the National Institute of Infectious Diseases identified a need for public health systems to use strategies with detailed managerial approaches.
- It would not be feasible to assess these by randomizing some hospitals to use them and others not to do so.
- Instead, they might be evaluated by comparing future data with the data from 2017.

# **Case study:** *Planning an evaluation of strategies that would be implemented in a future health emergency (3)*

- Such a study would collect information on dengue cases, outcomes for patients and use of hospital resources, including outpatient visits, admissions to hospital and bed occupancy before and during the next outbreak, for comparison with the 2017 findings.
- Need to consider whether the comparison of 2017 with the future epidemic was a fair comparison of "like with like" in relation to everything except the new strategies, including differences in data collection.

# Controlled before-after study

- **Controlled before-after study**: participants are in the intervention or the control group but the decision on which group they are in is not random or made by the researcher.
- Outcomes of people in both groups are measured before and after the intervention is introduced.
- Disadvantage: high risk of bias due to differences between the people in the intervention and control groups which may have influenced the group they joined and/or affect their outcomes more than the effect of the intervention.

# Interrupted time series

- **Interrupted time series design**: all participants receive the intervention and outcomes are collected at multiple time points, before and after it is introduced.
- Effect of the intervention is estimated by comparing the trend in outcomes after its implementation with the trend beforehand.
- Disadvantage: if any other features of the setting change close to the time that the intervention was introduced, it would not be known whether those changes may have affected the outcomes.

# Conclusions

- For centuries, decisions about health interventions were based mostly on personal experience, case histories and comparisons between entirely separate groups of people receiving different interventions.
- These sources of knowledge are still in use today, but the information they provide may be unreliable because of biases.
- More reliance is now placed on randomized trials and systematic reviews (see Chapter 2.6), which show if differences in outcomes between groups are due to the effects of the interventions.
- These allow decision makers to have greater confidence in the evidence when choosing interventions or setting policy.

# Key messages

- People choosing between different interventions, actions and strategies need reliable and robust evidence on their relative effects.
- This needs to come from research that has minimized the effects of bias and chance.
- Randomized trials test interventions in a way that ensures that any difference between the outcomes of the participants in the groups being compared are due to the effects of the intervention, or chance.

# Further readings

Clarke M, et al. What evidence is available and what is required, in humanitarian assistance? Scoping Paper 1. New Delhi: International Initiative for Impact Evaluation (3ie). 2014. https://www.3ieimpact.org/sites/default/files/2019-01/3ie_scoping_paper_1-humanitarian-top.pdf

Scoping paper providing information that should help researchers and others identify topics in the humanitarian sector that are likely to benefit from new research.

White H. An introduction to the use of randomized control trials to evaluate development interventions. Journal of Development Effectiveness. 2013; 5(1): 30-49.

Introduction to the use of randomised trials to evaluate interventions in the development sector.

# References

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**Uncertainty principle:** Peto R, Baigent C. Trials: the next 50 years. Large scale randomized evidence of moderate benefits. BMJ. 1998; 317: 1170-1.

**Minimisation:** Treasure T, MacRae KD. Minimization: the platinum standard for trials. BMJ. 1998; 317: 362-3.

**Blinding (masking):** Anand R, et al. Fool's gold? Why blinded trials are not always best. BMJ. 2020; 368: l6228.

**Managing dengue fever in Sri Lanka:** Rathnayake D, et al. Response of the National Institute of Infectious Diseases, Sri Lanka to an unexpected dengue epidemic in 2017. Ceylon Medical Journal. 2018; 63: 108-12.

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