Introduction to Clinical Research

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Nov 2023

Why Medical Research?

- The patient population trusts us to give them the best and latest about their illness and health.
- There are still and will always be questions unanswered you will be faced with specially when you start managing patients
- These questions can be properly addressed through research

Research Design

- You may hear about different types of study design and it may be confusing, but it can also be very simple
- Defining the study type tells us a lot about the limitations strengths the value of the outcome, what statistical tests and design we can expect etc..
- The simplest way to classify research is looking at it being Observational Vs Experimental

Research Design

- The whole idea is to reduce bias and try to find true cause and effect.
- Observation Research inquires about status quo and assesses what we do routinely.
- Experimental Research We intervene with Status quo and assess our intervention with a drug, procedure, training etc..
- The more we decrease the bias the closer we are to a real cause and effect finding

EUPATI
European Patients' Academy on Therapeutic Innovation
www.eupati.eu

Evidence Based Medicine and Levels of Evidence

Observational Studies

- Examples:
- Case Report and Case Series
- Case Control Studies (Retrospective)
- Cross Sectional Studies (Surveys)
- Cohort Studies (Prospective)

Case Report and Case Series

- A case series is perhaps the simplest of all study types and reports a simple descriptive account of a characteristic observed in a group of subjects. It is also known by the terms clinical series or clinical audit.
- A case series:
- observes and describes subjects
- can take place over a defined period or at an instant in time
- is purely analytical and requires no research hypotheses
- is commonly used to identify interesting observations for future research or planning

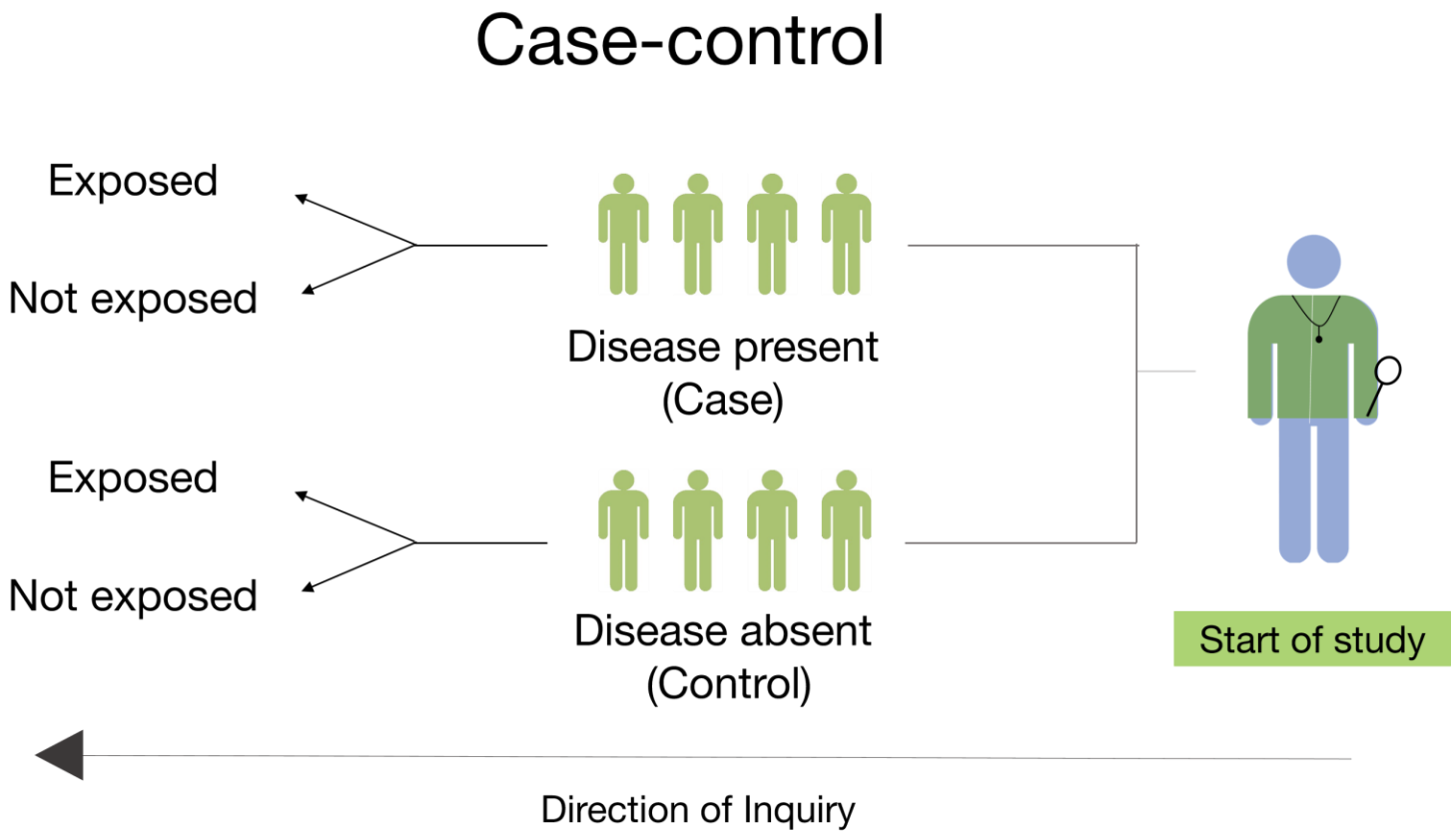
Case Report and Case Series

- HIV Encephalopathy: pediatric case series description and insights from the clinic coalface
- Kirsten A Donald,corresponding author Kathleen G Walker, Tracy Kilborn, Henri Carrara, Nelleke G Langerak, Brian Eley, and Jo M Wilmshurst
- Abstract
- Background
- The Human Immune Deficiency Virus (HIV) can manifest neurologically in both adults and children. Early invasion of the central nervous system by the virus, affecting the developing brain, is believed to result in the most common primary HIV-related neurological complication, HIV Encephalopathy (HIVE). In countries such as South Africa where many children have not been initiated on antiretroviral treatment early, HIVE remains a significant clinical problem.
- Methods
- Children were selected from a clinic for children with neurologic complications of HIV, located at the Red Cross War Memorial Children's Hospital, South Africa 2008–2012. Eligible subjects fulfilled the following inclusion criteria: aged 6 months-13 years; positive diagnosis of HIV infection, vertically infected and HIVE as defined by CDC criteria. Each participant was prospectively assessed by a Pediatric Neurologist using a standardized proforma which collated relevant details of background, clinical and immunological status.
- Results
- The median age of the 87 children was 64 months (interquartile range 27–95 months). All except one child were on antiretroviral treatment, 45% had commenced treatment <12 months of age. Delayed early motor milestones were reported in 80% and delayed early speech in 75% of children in whom we had the information. Twenty percent had a history of one or more seizures and 41% had a history of behavior problems. Forty-eight percent had microcephaly and 63% a spastic diplegia. CD4 percentages followed a normal distribution with mean of 30.3% (SD 8.69). Viral loads were undetectable (<log 1.6) in 70% of the children. Brain imaging was performed on 56% with 71% of those imaged demonstrating at least one abnormality, most commonly white matter volume loss or signal abnormality.
- Conclusions
- Amongst the cohort of children referred to this clinic, the diagnosis of HIVE was unrecognized in the general medical services, even in its most severe form. Developmental delay and school failure were major presenting problems. Co-morbidities are a frequent finding and should be sought actively in order to optimize management and promote best possible outcomes for this vulnerable group of children.
- Keywords: HIV encephalopathy, Children, MRI, Brain, Developmental delay

Case Control Studies (Retrospective)

- **Case-control studies**
- selects subjects on the basis of a presence (cases) and absence (controls) of an outcome or disease
- looks back in time to find variables and risk factors that differ between groups
- can attempt to determine the relationship between the exposure to risk factors (or any measured variable) and the disease
- case-control studies can include more than two groups

Case Control Series (Retrospective)



Cross Sectional Study (Surveys)

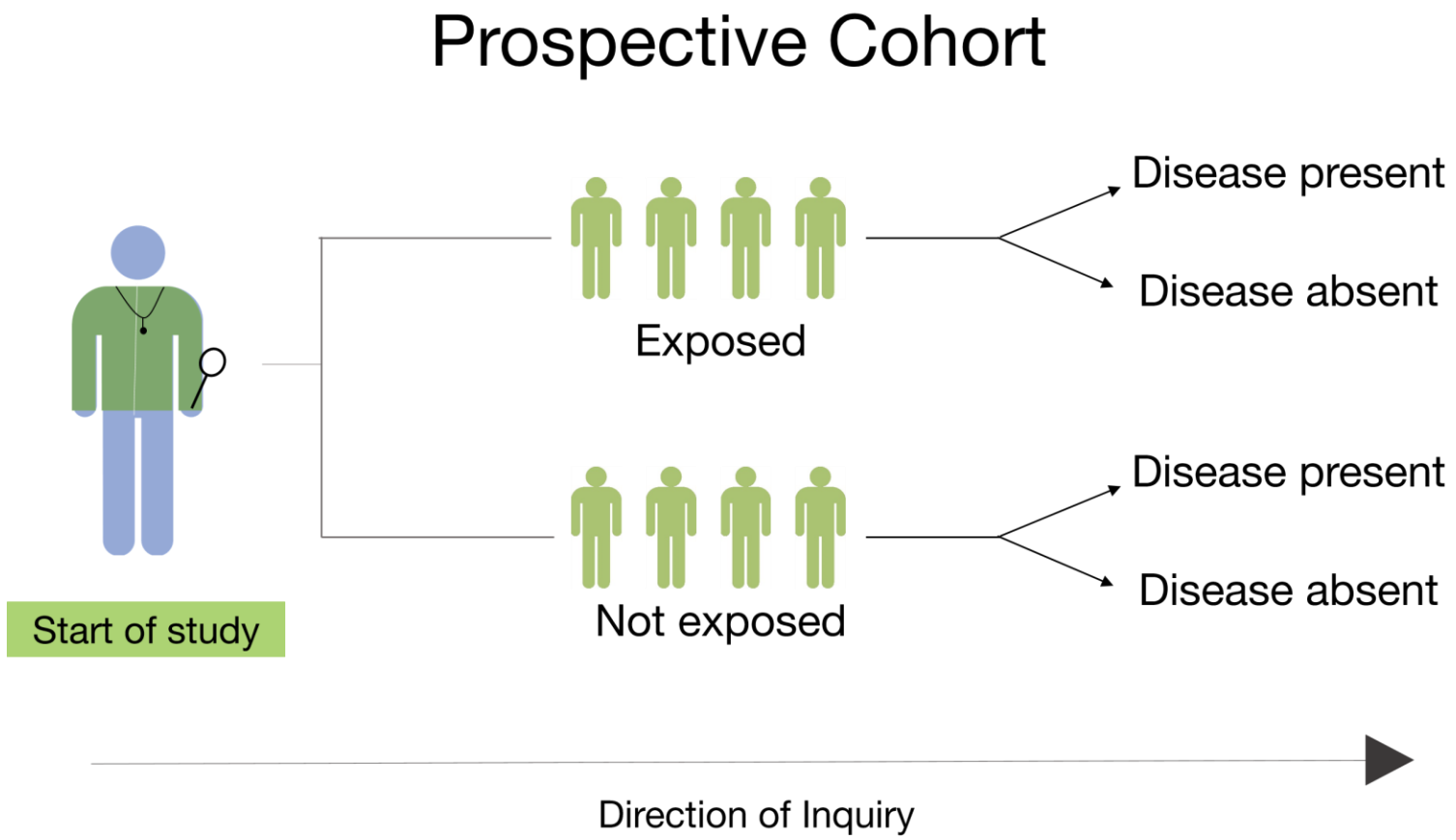
- **Cross-sectional studies**
- identifies a population or sub-population rather than individuals
- takes place at a point in time or over a (relatively) short period
- can measure a range of variables across groups at the same time
- is often conducted in the form of a survey
- can be a quick, easy and a cost effective way of collecting information
- can be included in other study designs such as case-control and cohort studies
- is commonly used to measure prevalence of an outcome or disease, i.e. epidemiological studies

Cohort Studies (Prospective)

- **Cohort studies**
- begin by identifying subjects (the cohort) with a common trait such as a disease or risk factor
- observes a cohort over time
- Usually collected Prospectively

- In a prospective cohort study, the researcher identifies subjects comprising a cohort and their exposure status at the beginning of the study.
- They are followed over time to see whether the outcome (disease) develops or not.
- This usually allows for better data collection, as the actual data collection tools are in place, with required data clearly defined.

Cohort Studies (Prospective)



Experimental Studies

- Control
- Randomization
- Blinding

- The gold standard of these designs is a double blinded randomized and placebo-controlled trials : can give the strongest evidence to prove causation.

Meta Analysis and Systematic Reviews

- The highest level of medical evidence
- It is a masterpiece if done correctly: summarizes literature, performs analysis and Combines qualitative and quantitative review
- May include meta analysis and expert opinion

Meta Analysis and Systematic Reviews

- An exhaustive effort : PRISMA guidelines
- Looks at all publications related to a topic
- Looks at the results of all these studies and try to see if the combined results center around a common measurement, combining studies of low power together to achieve statistical significance
- Con: Publication Bias

Good Clinical Practice (GCP)

What is GCP

Acquiring a GCP Certification

Where do we Start?

- Start with a **Research Question**
- Preliminary Study Design
- Conduct a **Literature Review**
- Finalize :

1. Study Design
2. Primary and Secondary Objectives
3. Statistical Plan

From Proposal to Publication

- Write a Study **Protocol or Proposal, Questionnaire, Informed Consent, Case Record**
- Submit to your **IRB and get approvals**
- **Collect Data**
- **Data Analysis**
- **Manuscript Writing**
- **Submission to a Journal**

Research Work is Team Work

- It is very important right from the beginning to identify the research team.
- Usually there is a primary investigator who leads the whole research project, gives mentorship and final feedback on the proposal and the manuscript and the submission journal in addition to putting preliminary timelines.
- The roles and responsibilities of the rest of the team members must be identified and a confidentiality statement should be signed by team members.
- In case of publication the author names and sequence should be agreed upon among the team members.
- There could be a resident team leader coordinating the work of the team and following the timelines and coordinating with the mentor.

Coming up with a Research Question

- Questions to be answered are encountered every day in our practice
- Identify an area of passion and or an area of information gap
- The quickest way to get data is the cross sectional surveys and from there you can move into either a retrospective, or prospective design
- If you encounter an interesting case, a rare, or refractory case that eventually responded to your management then case report
- Try during residency at least one systematic review

Literature Review

- Look at the research question from available databases.
- The free open access ones are: Pubmed and google scholar
- Include your key words and perform a search (these are called MESH words) and Boolian logic
- You may also use the usual Google engine to look for grey literature

Writing Your Research Proposal

- Finalize your question, objectives and statistical plan.
- Write your proposal and ask for your institutional proposal form
- Design your Case Record Form if your study is a retrospective or prospective or experimental study
- Design your survey if your study is a cross sectional survey study with the first section including study information, consent and confidentiality statement
- Design your patient informed consent if there is prospective data collection or an experimental design

Submission Process and the Waiting Game

- When you submit your research to get IRB approval use this time to target your journal of choice.
- Look at the Notes to Authors
- Start Drafting your Abstract with the Following sections:

1. Introduction
2. Aim
3. Methodology

- Start Drafting your Manuscript with the following sections:

1. Introduction
2. Methodology

Bonus Preparation

- Prepare what tables you want
- Prepare what graphs you want
- Prepare an electronic version of your case record form (may use google forms which immediately transfer data to an excel sheet)
- Choose a statistician from the beginning

Post IRB Approval

- Start your data collection using your electronic format
- Once data collection is complete continue to data analysis
- Fill in your tables

Manuscript Writing

- By this time you would have identified your journal of interest, read the notes to authors drafted half an abstract and half a manuscript.
- Write up the results section in the manuscript and abstract
- Write up the discussion section, conclusion, limitations and recommendations in the manuscript
- Write up the conclusion section in the abstract section.

Manuscript Review and Editing

- Review your manuscript with your research mentor
- Edit the manuscript based on your mentor s recommendation.
- Get your final version approved by the mentor and submit to a journal.

Research Visibility

- Submit your abstracts to local regional or global scientific meetings.
- Looking at the success of the University of Jordan Graduation Research Project and the creation of an institutional Scientific Research Day where residents can present their research as oral or poster presentations and the institution can celebrate this achievement with invitation to all staff members and external guests related to the medical field.

“Team Work Always Works!” Dr. Ayman Hammoudeh

- Success is a multi collaborative process
- Advice to submit to the highest possibly ranked journal and if rejected get feedback and incorporate into the study and resubmit to another journal.
- Good Luck ☺