Ethical issues in Paediatric Observational studies

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Objectives

- What are observational studies
- The social importance
- The scientific importance
- Ethical issues
- The role of the Paediatrician

Definition of observational studies

- **Observational** study which observes people in different circumstances over which the researcher has no control
- A type of study in which individuals are observed or certain outcomes are measured.
- No attempt is made to affect the outcome or data is modified
- Settings is naturalistic not modified, naturally occurring situations

Observational studies

- Observational studies can be based on documentation in archived health records or patient databases maintained by states, insurers, departments or researchers, retrospective or created prospectively.
- Cross sectional/ longitudinal
- Nonroutine interventions may have been unplanned or designed prospectively.
- The observations may be reported individually, or in aggregated and analysed forms.

Need for observational studies

- Experimental studies is unnecessary

When the effect of an intervention is dramatic, the likelihood of unknown confounding factors being important is so small that they can be ignored
Examples: insulin for diabetes, immobilisation for fractured bone

Need for observational studies

- Experimental studies is unnecessary
- Experimental is inappropriate

Small numbers

Example: post marketing surveillance, bile duct damage after lap cholecystectomy

Difficulty in assessing the preventing of rare events following the interventions

Example: placing babies prone/supine to prevent SIDS- need very large numbers

Outcome interests are far in the future

Examples: long term complications of OCP, hormone replacement and fracture femur

in these situations retrospective studies can be done

Need for observational studies

- Experimental studies is unnecessary
- Experimental is inappropriate
- Experimental is impossible

Reluctance and refusal of the clinician to participate *
Ethical objections
Political and legal obstacles
The task itself

Need for observational studies

- Experimental studies is unnecessary
- Experimental is inappropriate
- Experimental is impossible
- Experimental is inadequate

Low external validity **
Patients may be atypical
Poor recruitment rate
Generalising the results may be atypical
Pragmatic trials that evaluate normal clinical practice is better

Types of observational studies

Cross-sectional study

- looks at a population at a single point in time.
- It examines the relationship between exposure and outcome prevalence in a defined population without regard to changes over time
- Researchers take a measurements (e.g., of a health condition or problem and a factor they believe to be related) at a single point in time –
  - A snapshot
- There is no review of past circumstances, knowledge of whether the exposure came before the outcome, or observation of change over time.
- Means, SD, Percentages, regression, OR

Types of observational studies

Case-control study

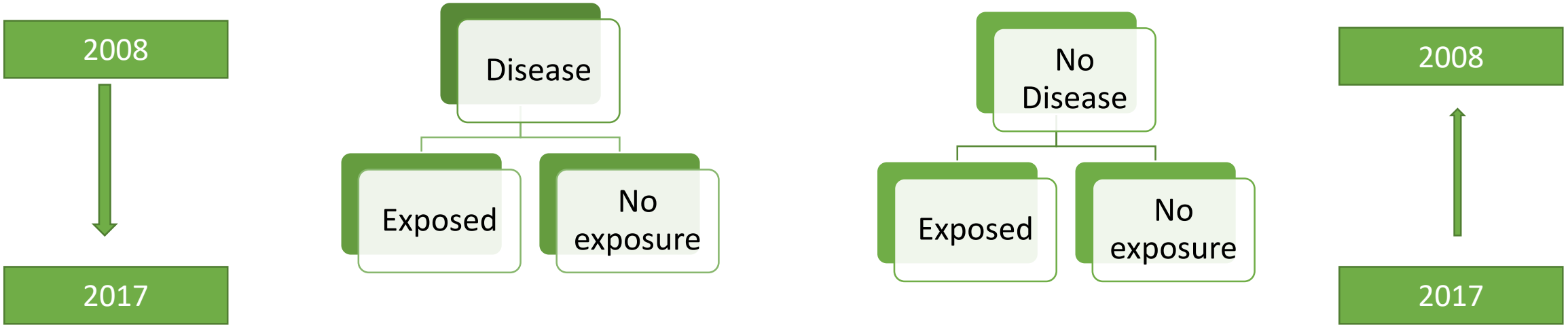
- Are retrospective studies/prospective
- Typically examines multiple exposures in relation to an outcome; subjects are defined as cases and controls, and exposure histories are compared
- Study subjects are identified and enrolled as either having, or not having, a given outcome
- Researchers then look back into subjects' history (usually by reviewing records or relying on subject' recall) to learn about their exposure status.
- As researchers are reviewing events that happened in the past, Generally, researchers enrol two to four times more controls than cases.
- Major problem is selection bias – eg patients from tertiary centre
  - More controls can minimise this

Types of observational studies

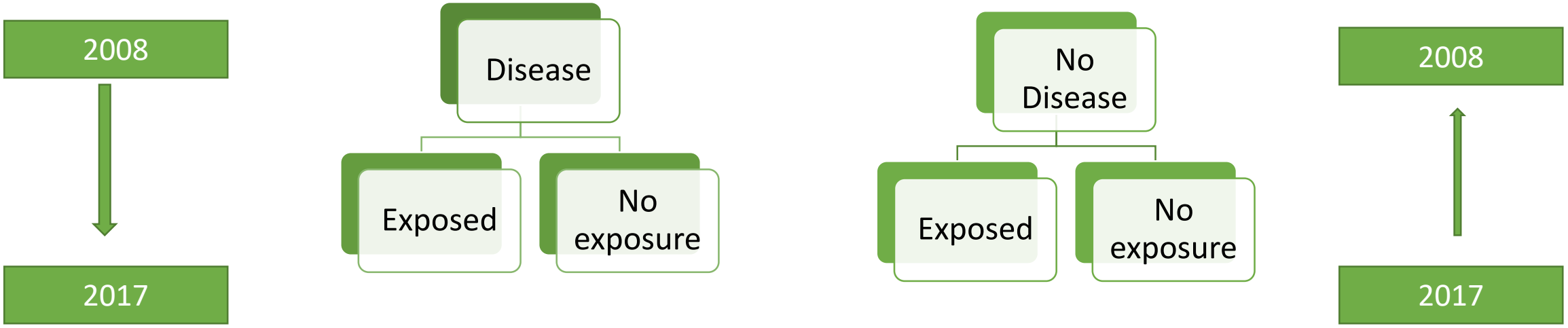
Cohort study

- Typically examines multiple health effects of an exposure; subjects are defined according to their exposure levels and followed over time for outcome occurrence
- Another term for a cohort study is a longitudinal study.
- Study subjects are identified and enrolled as either being *exposed* or not
- They are then followed to determine whether they develop the associated outcome.
- Cohort studies can be prospective or retrospective.
- Prospective studies recruit subjects based on exposure status and follow them to observe the health outcomes of the exposure.
- Retrospective studies begin after outcome occurrence has already taken place, but look back at effects of an exposure on an outcome and still classify subjects based on their exposure status.

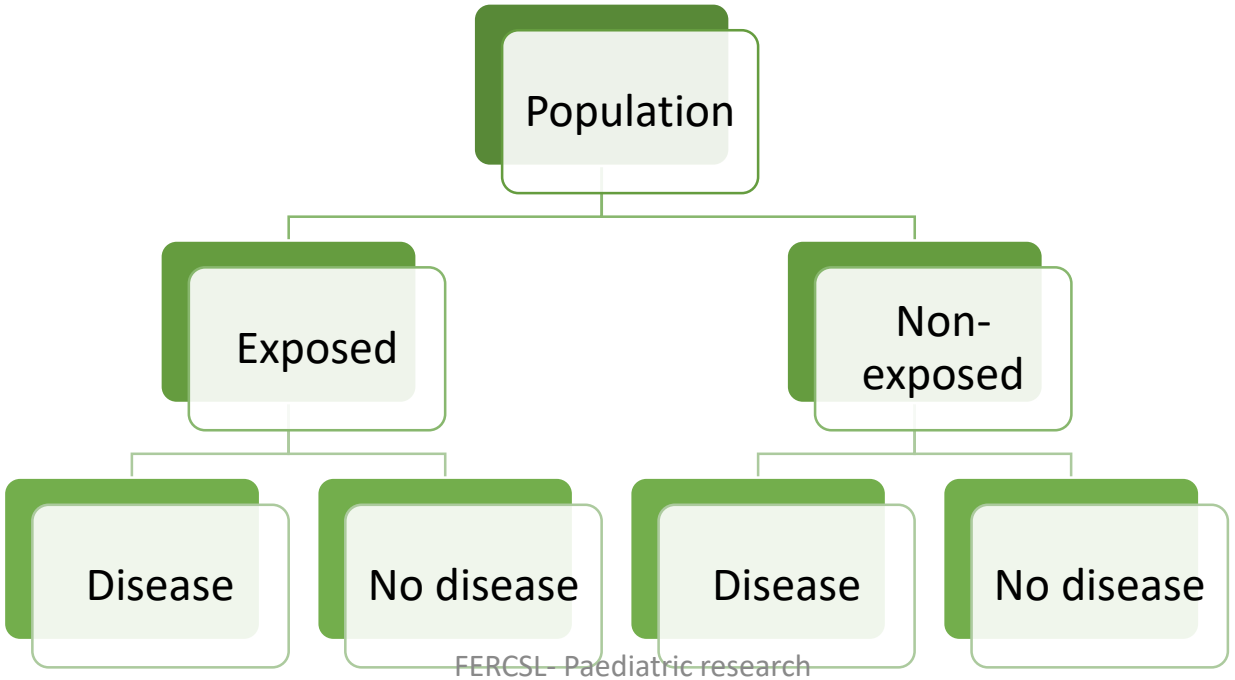
Case control



Case control



Cohort



Types of observational studies

- Case reports
  - Reports of cases from health or disability services or research settings.
- Case series
  - Describe a set of cases of a disease (or similar problem).
  - For example, a clinician may assemble a case series on a topic of interest, unexpected adverse effect, unusual presentation
- Descriptive studies
  - Examine the existing distribution of variables in populations
  - Analyses of cancer registry data or emergency department data by person, place or time.

Types of observational studies

Ecological study

- Examines the relationship between exposure and outcome by examining population-level data rather than individual-level data
- Researchers look at aggregate data for a population (for example, a nation) to review trends and make observations about a health condition or problem on a large scale.

Definition	Advantages	Disadvantages
Cross sectional		
Examines relationship between exposure and outcome prevalence in a defined population at a single point in time	Less time-consuming than case-control or cohort studies Inexpensive Good, quick picture of prevalence of exposure and prevalence of outcome	Difficult to determine temporal relationship between exposure and outcome (lacks time element) May have excess prevalence from long duration cases (such as cases that last longer than usual but may not be serious) High refusal rates
Case control		
Examines multiple exposures in relation to an outcome; subjects are defined as cases and controls, and exposure histories are compared	Relatively inexpensive Less time-consuming than cohort studies Can evaluate effects of multiple exposures Efficient for rare outcomes or outcomes with long induction or latency periods	Subject to recall bias (based on subjects' memory and reports) Difficult to establish clear chronology of exposure and outcome Cannot estimate incidence and prevalence

Study type	Advantages	Disadvantages
Cohort		
Examines multiple health effects of an exposure; subjects are defined according to their exposure levels and followed over time for outcome occurrence	Can evaluate multiple effects of a single exposure More efficient for rare exposures and outcomes with long induction and latency periods Can directly measure incidence Clear chronological relationship between exposure and outcome	Expensive Time-consuming
Ecological		
Examines relationship between exposure and outcome with population-level rather than individual-level data (usually defines groups by place, time, or both)	Inexpensive Less time-consuming Simple and easy to understand Examines community-, group-, or national-level data and trends	•Subject to the ecological fallacy, which infers association at the population level whereas one may not exist at the individual level •Difficult to detect complicated exposure-outcome relationships

Scientific validity of observational studies

- Building the evidence for best practice
- Identifying the types, frequency, and severity of errors and adverse events in health care.
- Precision-lack of random error or random variation in a study's estimates
  - A large standard deviation relative to the estimate indicates low precision.
  - Wide confidence intervals for estimates of association (e.g., odds ratios or relative risks) indicate low precision.
- Validity - lack of systematic error
  - Internal validity refers to the strength of the inferences from the study - low
  - External validity is the ability to generalize study results to a more universal population - high

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Validity	Experimental	Cross sectional	Cohort	Case control
Internal	High	Low	Low	Low
External	Low moderate	High	High	High

Scientific validity of observational studies

- Statistical methods
  - Use of odds ratio and chi square – only appropriate for linear relationships
  - Regression is better when multiple variables are compared
  - In 2x2 data use of relative risk is better than OR
- Evidence to support causation
  - Statistical methods
  - Internal and external validity
  - Biological plausibility
  - Confirm with experimental evidence

Social value of observational studies

- Public is entitled to a safe and effective health care services
  - Examine an exposure to the diseases
  - Effectiveness of a treatment
- Further the understanding of the disease spectrum
- To identify deficiency in health or disability support services and can be acted on
- Help to give consumers details of the measures taken to protect participants from harm
- Help to make policy and regulatory decision

OS will be "unethical" if done "non scientifically”

- Major challenge
  - Study design and tool – questionnaire, sample size and sample method
  - Selection bias – differ in their baseline characteristics
  - Confounding - For a factor to be a confounder, it must differ between the comparison groups and predict the outcome of interest
    - Age and sex are matched but not attitudes, beliefs and motivation which can confound the treatment
    - Overcome by study design and analysis – applying regression
  - In Cohorts lost for follow-up
  - Random measurement error
    - More in retrospective studies
    - Observational cohorts reduce this
    - Blinding the person who assesses the outcome as the patient and physician are aware of the experiment and the expected outcome

OS will be "unethical" if there is no social value

- Duplicating the study
- Unimportant results
- Under reporting
  - To report use check lists
  - STROBE/CONSORT

The ethical aspects

Underlying ethics
Respect for people
Study design and protocol
Collection of information
Consent
Confidentiality

The need for ethical clearance from ERB

- Investigators conducting, or involved in conducting, observational studies are responsible for ensuring these studies meet ethical standards
- The principal investigator is responsible
- The Standard Operating Manuals (SOP) will help
- Advice from the ERB

Respect for people

- Autonomy
- Requires that people who are capable of deliberation about their personal goals should be treated with respect for their capacity for self determination

- Protection of people with impaired or diminished autonomy, which requires that people who are dependent or vulnerable be afforded security against harm.

Justice

- Within a population, there is a fair distribution of the benefits and burdens of participation in a study
- Participant, a balance of burdens and benefits
- How to achieve this:
  - Avoid imposing on particular groups an unfair burden of participation in research: patients at THJ, certain MOH areas
  - Clear inclusion and exclusion criteria
  - Not discriminate in the selection and recruitment of participants by including or excluding them on the grounds of language spoken, ethnicity, age, sex, disability or religious or spiritual beliefs

Beneficence and non-maleficence

- Risk is reasonable in the light of benefits
- Proportionate care – greater risk more care addressed in ethical issues
- Protection of participants
  - Potential harms are minimal
    - Less or no intervention
    - Less dependent relationship with the investigator
  - Breech in confidentiality

Integrity

- An investigator’s commitment to the advancement of knowledge implies
  - A duty to conduct honest and thoughtful inquiry
  - Rigorous analysis
  - Be accountable for her or his activities.

Diversity

- Investigators doing observational studies
  - Understand, respect and make due allowance for diversity among participants and their communities

Conflict of interest

- Investigators should identify to co-investigators, sponsors, employers, participants and, where applicable, ethics committees any perceived, potential or actual conflict of interest he or she might have in relation to any others who are involved with the study.
- Such conflicts of interest can compromise the design or conduct of a study or the reliability of its results, thereby exposing study participants or others to needless risk or inconvenience.
- As appropriate to the circumstances, any conflict of interest should be minimised.

Design of study and protocol

- Study question
  - Important health problems
  - Ensure a potential improvement of the health outcomes
  - Reduce inequalities

- Study design
  - Minimise risk of harm
  - If possible to involve community participation in planning and conduct of research

Design of study and protocol

- Scientifically sound
  - Scientific validity is an important component of good ethical practice in research
  - The scientific quality of a proposal should be such that the proposal's objectives can reasonably be expected to be achieved.
  - For example, a questionnaire unlikely to achieve an adequate response rate will be scientifically inadequate
  - Every study proposal must be based on a thorough review of relevant current literature.
  - Independent peer review will optimise scientific validity
- Skills and resources
  - Possess skill in that field to deal with problems that occur with participants
  - Professional standards
- Written protocol

Fair subject selection

- Determined by the inclusion and exclusion criteria
- Selection, recruitment, retention
  - Distribute burdens and benefits fairly
  - Ensure social value of research
  - Enhance scientific validity
  - Minimize risks to subjects
  - Enhance benefits to subjects
  - Protect the vulnerable
    - Children
    - Subjects lack the capacity to make autonomous decisions
    - Unduly influenced
    - Coerced into participation
    - Provider might threaten to withdraw services unless a client participates in a study, or a student might enroll in a study due to fear of receiving a poor grade in a class.

Data collection - Types of data

Primary data	**Secondary data**
Advantages Investigator controls all aspect All variables of interest can be measured	Advantages Relatively fast and inexpensive Sample size tend to be large Can assess national trends
Disadvantages Time consuming Expensive	Disadvantages Data may not include all variables of interest Maybe difficult to understand how and why data elements were collected

Data collection

- Study information has to be provided – participants and non participants
  - Design
  - Who will have access to data
  - Contact details of person
- Identifiability
  - whether the individual concerned is ‘identifiable’ from the information
  - Types:
    - Identified
    - Potentially identifiable - coding
    - Partially deidentified – initials but reversible and irrversible
    - Anonymous

Data collection

- Method to collect the data
  - Registers/databases/records
  - Direct interviews
    - Properly trained personal
  - Telephone/online – prior notice has to be given
  - If the health practioner is not involved in the research permission must be sought from him/her

- Consent

Consent

- Informed consent:
  - Adequate understanding
  - Decision is voluntary
  - Disclosing the hypothesis
    - Results can be biased
    - If specific information cannot be given can inform as it will be revealed with results
  - The right of any person to decline to take part in a study or to withdraw from the study at any time must always be explained and respected
  - When a study involves people in dependent or unequal relationships, the investigator must ensure that their refusal to participate in, or decision to withdraw from, the study will not result in discrimination, a reduced level of care or any other disadvantages

Consent

- People with diminished competency to give consent
- Consider
  - Vulnerability
  - Injustice
- Obtained from legal representative

Consent

Inducement

- Investigators may seek to create legitimate motivation for participation in studies, but may not exert pressure by offering inappropriate inducements.
- Risks involved in participation should be acceptable to participants even in the absence of inducement
- It is acceptable for investigators to repay the incurred expenses of participants (Eg: travel costs)

Consent

- Documentation
- Evidence of free and informed consent
- When written consent is culturally unacceptable or good reasons exist for not recording consent in writing (anonymous data collection or telephone interviews)
- Implied consent – if a form is filled and sent
- Consent not needed
  - Potentially identifiable data
  - Impossible in data from records
  - Unnecessary anxiety

Can parents give consent

- Parents asked for permission for a child's participation in clinical research are often making decisions under great stress and time pressure.
- Some prefer to trust the physician's assessment rather than make their own
- Involving children in discussions and decision making respects their emerging maturity, helps them prepare for participation in research, gives them an opportunity to express their concerns and objections and, possibly, allows them to influence what happens to them

Confidentiality

- ‘Confidentiality’ is the respectful handling of information disclosed within relationships of trust, especially as regards further disclosure
- If disclosed may cause harm or distress
- Investigators should arrange to protect the confidentiality
  - Omitting identifiable information
  - Limiting access to data
- Maintain physical and electronic security
- Practice coding
- In participants involved in illegal activity – inform the participant

When to reveal information

- Health problem previously unknown to the individual is identified
- Arrangement of referral is done with the participants consent
- If a court of law requests the details
- If confidentiality is breached the investigator should be responsible to inform the participant

Respect for children and parents

- Consent process
  - Under 16 years cannot give consent
  - Accent
  - Not one off process but continuous
  - Slightest sign of unwillingness must be able to withdraw – say no, show no, pulling away, ignoring
- Retrospective consent
  - For some studies, most often observational studies, obtaining consent from all participants before you start may compromise the quality of the research
- Incentive – decided by the research team, travel/lost wage can be reimbursed
- Good practice to have a version of the final report written specifically for the children who participated on the research

Concerns

- Routine care Vs research
- The boundary is not clear
  - Data gathering:
    - Gathering of data beyond those required solely for clinical purposes,
    - The alteration of clinical practices in a way that is instrumental for the research,
    - Intent to publish the results
- Parental concerns
  - What will happen if my child doesn't participate
  - What will I be told during the study and after it is finished
  - How can I withdraw my child from the study
  - Will that affect my child's care
  - Who will know that my child is in the study
  - What information will they get
- Children's concern
  - No one seems to mind me/taking note of me
  - I am not important here

Paediatrician's role

- Understand the need for research
- Safe guard children
- Effective communication through out
- Practice evidence based medicine
- Avoid being reluctant due to ownership


THANK YOU!