Before You Begin: Key Issues to Consider

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Disclosures

- Consulting work for EMD Serono, Merke and Ferring
- Commissioned and voluntary work for Agency for Human Reproduction Canada

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Disclosures

- I’m a clinician
- Been at McMaster in Hamilton for about 20 years,after UK and Aus
- Have MSc in health research methodology
- Founding co-editor of Cochrane subfertility group
- Strong interest in clinical trials

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Objectives

- Why bother doing research at all?
- What's worth studying?
- How to define your question?
- Matching study architecture to the question
- Researching the "background"

Why bother?

"The whole of medicine depends on the transparent reporting of clinical trials"

*Drummond Rennie**

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Research is like art….

- Quality is everything

✓Commitment
✓Collaboration, skill
✓Communication
✓Planning
✓Time

So why bother?

- Its “fun”
  - Satisfying
- It makes a difference to practice
  - Yours and everyone else's
- It keeps you growing and connected
  - You really do meet interesting people
- It can be your career if you want
  - Staves off boredom and Alzheimer's

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What's worth studying?

- "Most of the knowledge and much of the genius of the research worker, lies behind his (her) selection of what is worth observing…

  It is a crucial choice, often determining the success or failure of months of work, often differentiating the brilliant discoverer from the... plodder".

  - *Alan Gregg, Canadian political pollster*

What's worth studying?

- Ask a ***useful*** question
  - Clinically relevant
  - Novel
- Ability to answer in a ***valid*** way
  - Appropriate study architecture
  - Rigorous study design and execution
- Make report effective, ***transparent***

What's worth studying?

- Feasible
  - Access to patients
  - Potential access to resources

To figure out what's worth studying?

- As a junior researcher, seek out a mentor
  - Your most important "choice"
  - He or she will help lead you in right direction
- As a senior researcher, iterate with your juniors and other peers
- Look for effective, generous people
- Consider formal research training
  - This will pay off many-fold

Worthwhile research is always a team sport

- Associate with productive well trained and widely published people
  - Surround yourself with people who know more than you do
  - Look for a job with a successful group
- Be prepared to share in work and kudos
  - Work your way up in a successful team

Summary - what's worth studying

- In many ways, the hardest choice to make; certainly the most important
- Easier when iterating with team
- Finding a good mentor is key
- Formal research training is denfinitely worthwhile - MSc in research methodology?

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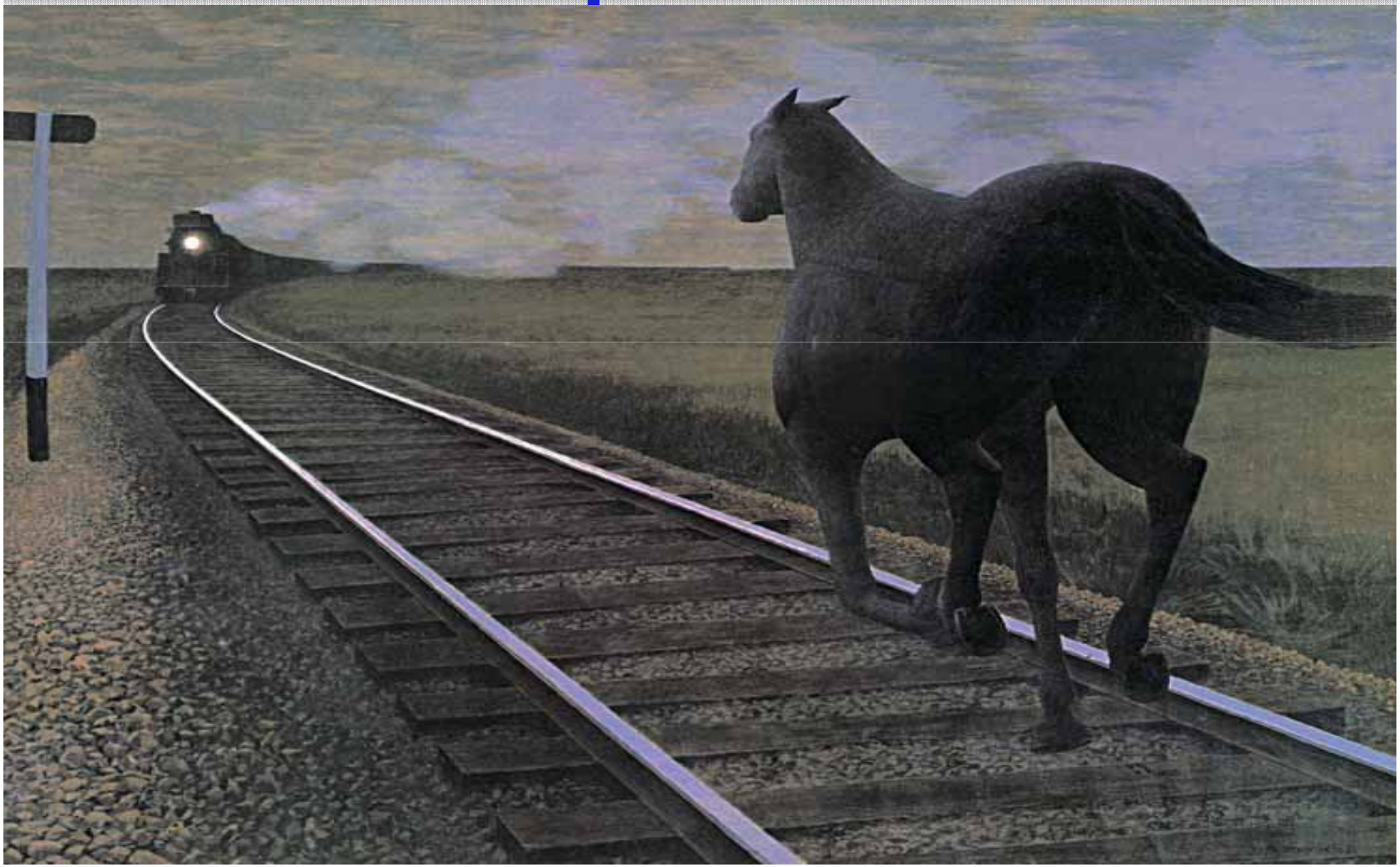
Formulating the question - why is that so important?

The question - why so important?



The question - prerequisites

- Relevant?
  - Will the answer make a difference?
- Novel?
  - Is the answer already out there?
- Explicit?
  - Is it clearly defined?
- Answerable?
  - Is it feasible, ethical, affordable to test?

Making the question explicit

- Population (sample)
  - “clinically relevant” and accessible?
- Intervention
  - ethical, affordable and accessible?
- Comparator
  - sensible, clinically appropriate, ethical?
- Outcome
  - Explicit and measurable?
  - Effect-size clinically and statistically significant?

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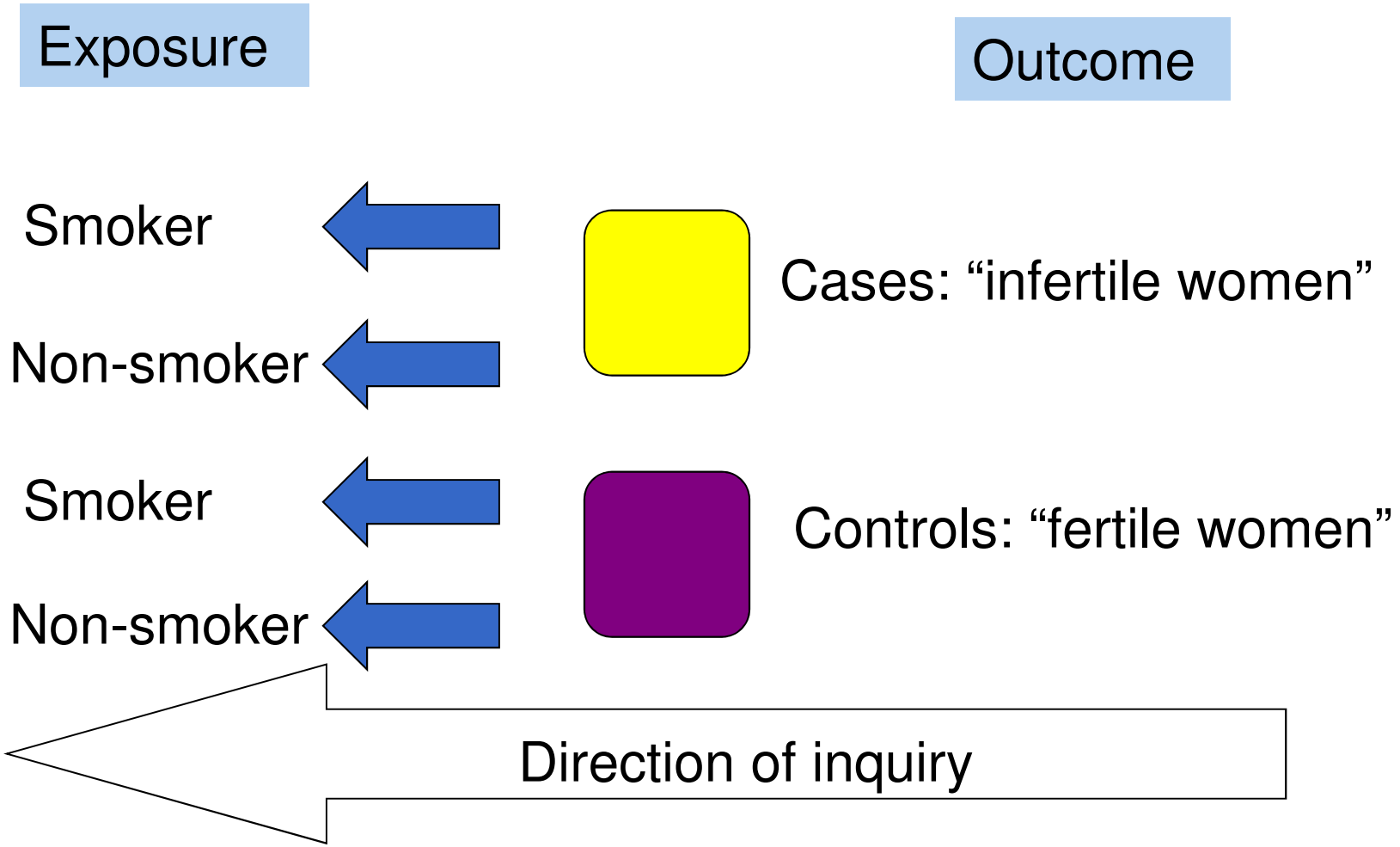
Choosing appropriate study architecture

- Retrospective studies
  - Observational - case control and “trohoc”
- Prospective studies
  - Observational - cohort
  - Experimental - RCT

Choosing appropriate research architecture

- Causation?
  - Case-control for rare disease
  - Cohort for “common” disease
- Diagnostic test?
  - (Cohort)
  - RCT
- Treatment?
  - (Cohort)
  - RCT

Case-control: does cigarette smoking reduce fertility?



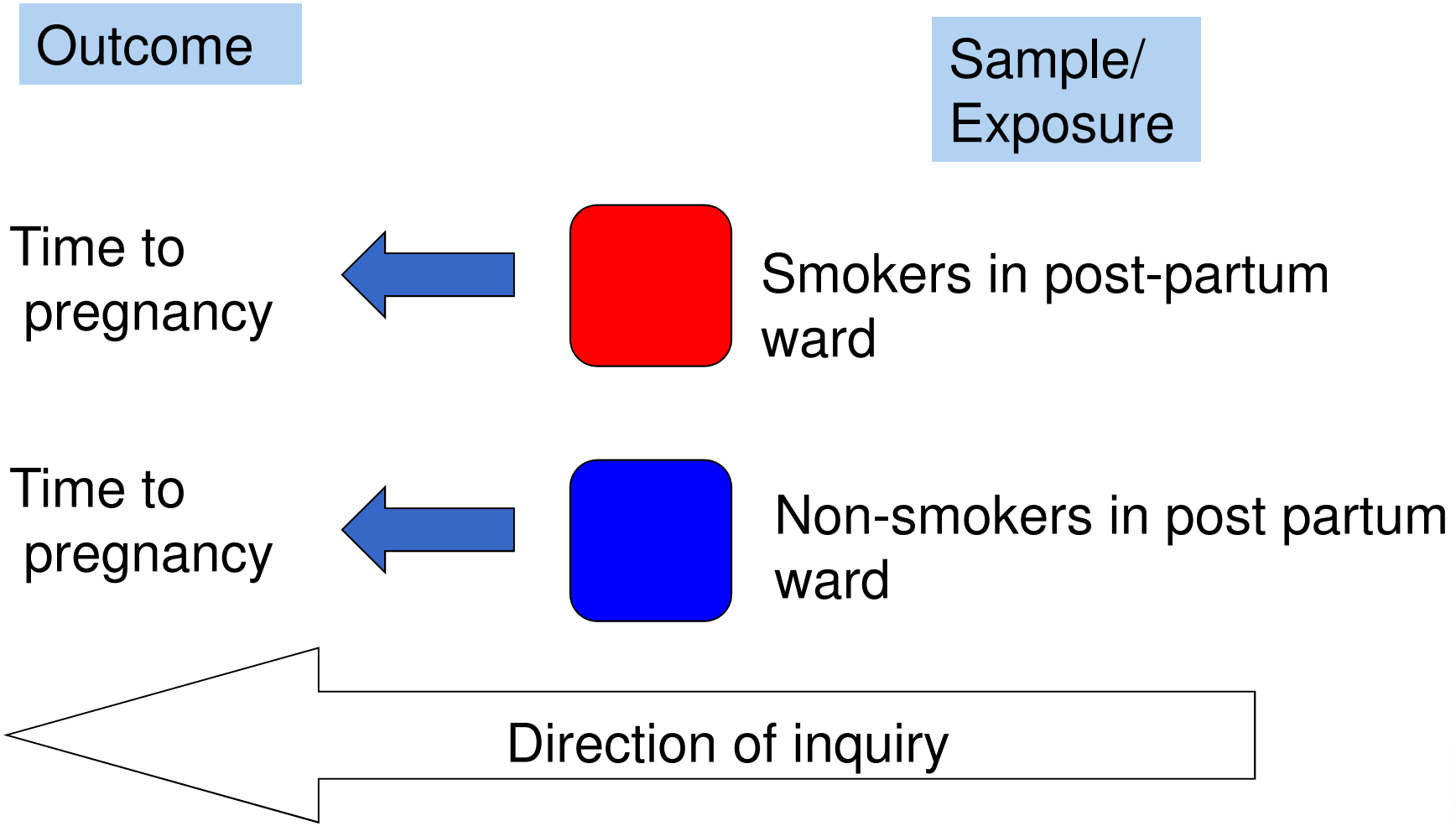
Case-control study

- Cheap
  - Chart review
  - Database search
- Quick
  - Data already available
- Easy
  - Design not complex

- Selection bias
  - confounders
- Recall bias
  - Disease jogs the memory

Hypothesis generating in most situations

TROHOC : does cigarette smoking reduce fertility?

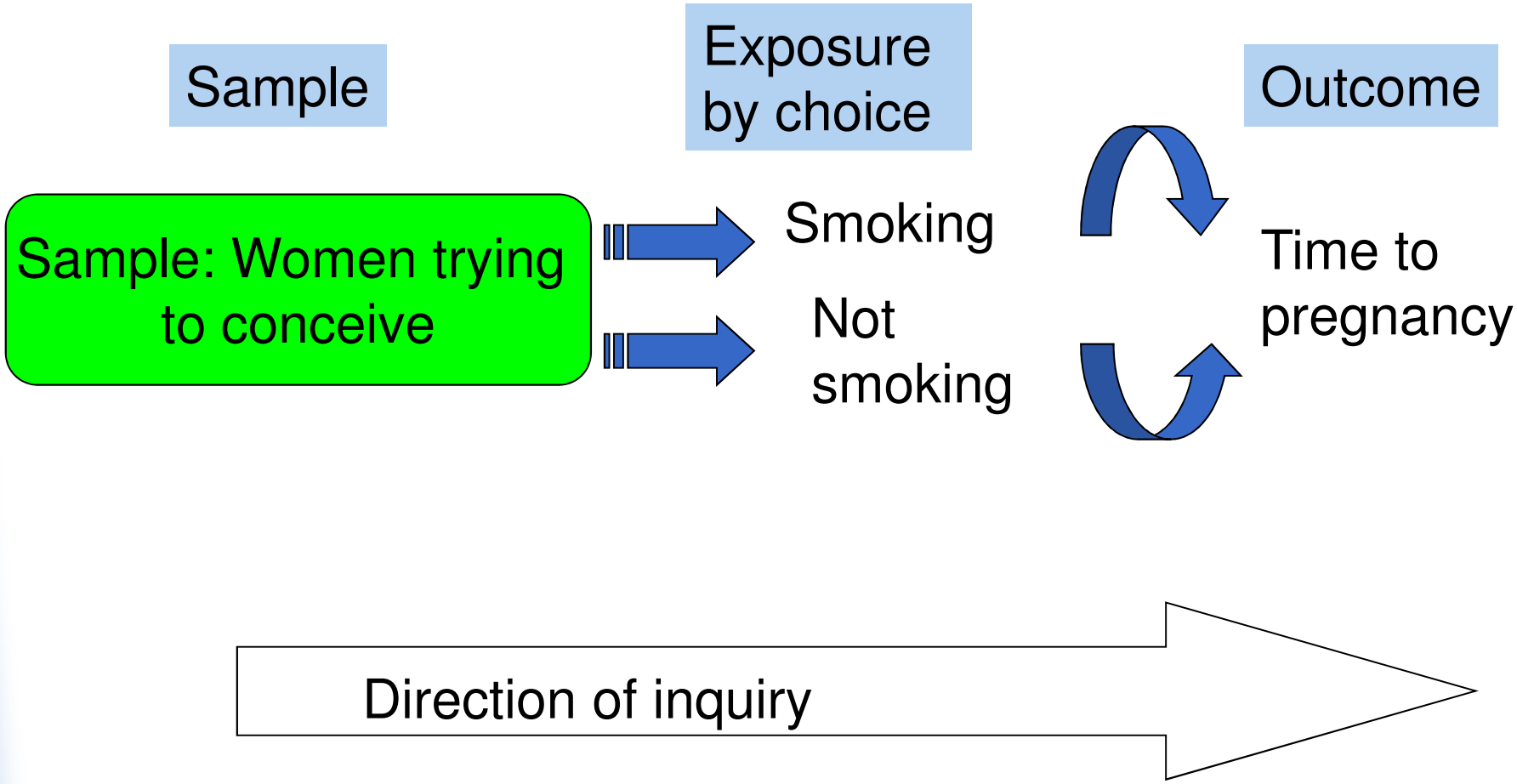


TROHOC study

- There is a sample!
- Exposure established first
- Outcome measure less biased?
- Cheaper, quicker than cohort design
- Still prone to “recall” bias
- Confounding likely between groups e.g. alcohol, caffeine
- Not useful for rare diseases

More robust than case-control, but not by much

Does smoking reduce fertility - cohort design



Cohort study

- Has a real sample
- Can measure exposure at outset
- Can measure some confounders
- Can capture outcomes with more certainty

- Impossible to adjust for for unknown confounders
- Expensive, long
- Not feasible for rare outcomes

Best possible design when randomization of exposure not feasible

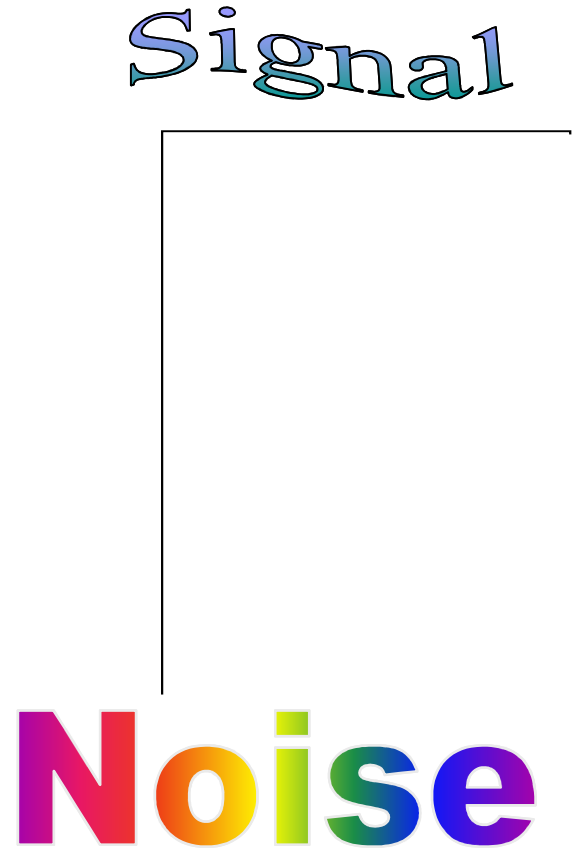
Observational studies work best with high “signal-to-noise ratio”

Smoking and Infertility

Observational studies work best with high "signal-to-noise ratio"

Smoking and Infertility

Smoking and lung cancer



Study architecture and built-in bias

- Smoking and lung cancer mortality:
  - RR from case-control studies 30
  - RR from cohort studies 10

Experimental design

- Exposure is by chance not choice
- Known and unknown confounders “evenly distributed” between groups
- Isolates signal from noise

Serial endometrial biopsy pre-IVF?

- In women with two unsuccessful embryo transfers, does a single luteal phase biopsy in the cycle before next transfer, increase the likelihood of success?

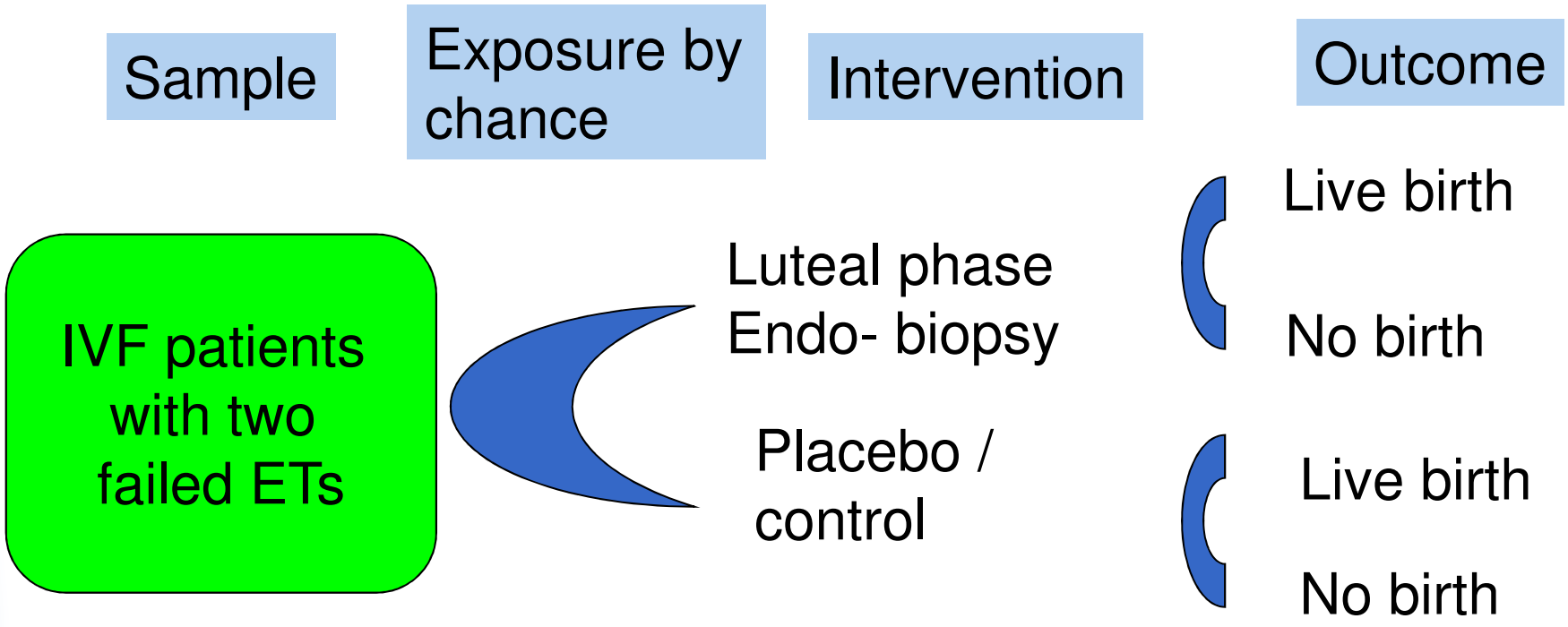
Serial endometrial biopsy pre-IVF?

- In women with *two unsuccessful embryo transfers*, does a single *luteal phase biopsy* in the cycle before next transfer, increase the likelihood of *success*?

Defining the question

- Population
  - One fresh and one frozen?
  - What if no frozen embryos - two fresh?
  - Age cutoff 39?
- Intervention
  - How many biopsies, when exactly, how done?
- Comparator
  - No biopsy, placebo / sham?
- Outcome
  - Implantation, clinical pregnancy, live birth?

Randomized controlled trial of endometrial biopsy pre-IVF



Design issues to consider

- Defining population (sample)*
  - How many prior transfers?
  - Fresh or frozen?
  - Age and other prognostic factors?
- Defining intervention
  - How many biopsies?
  - When should they be done?
- Defining outcome
  - Live birth vs surrogates?

Clinical and statistical significance

- Specify the clinically important difference in “Methods”, as basis of power calculation
- Consider the practicality of the trial in terms of patient volume, eligibility criteria and potential for acceptance once invited

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Effect size?

- A difference, to be a difference, should make a difference

Gertrude Stein

Top sources of bias related to architecture

- Case-control
  - Recall bias
  - Confounding
- Cohort
  - Selection bias
  - Confounding
- RCT
  - Allocation bias
  - Publication bias*

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Researching the background

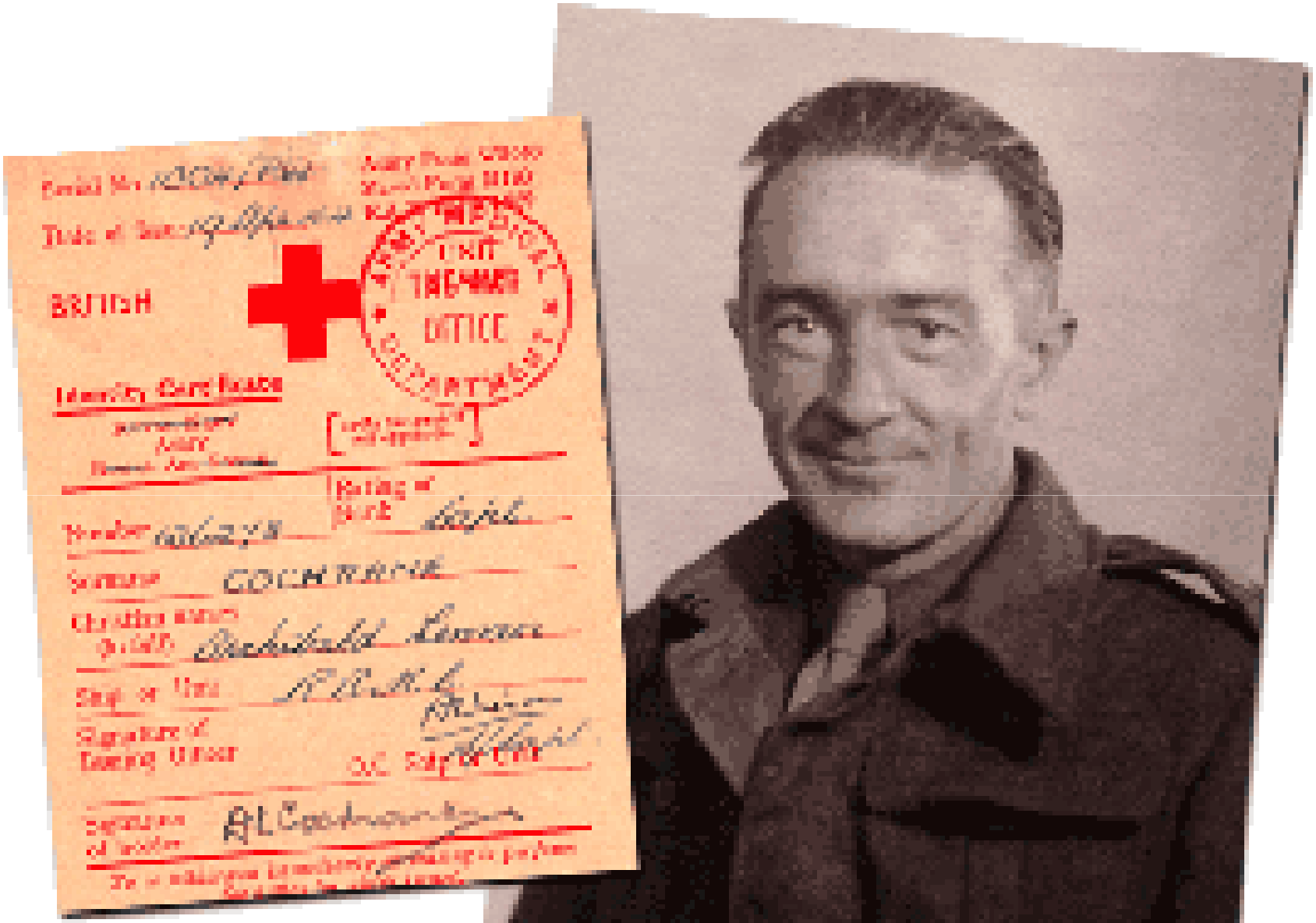
- Electronic search
- Seek trials / systematic reviews
- Look at bibliographies
- Extent of search depends on goal
  - Fleshing out idea?
  - Checking if definitive trial already done?
  - Putting together the study proposal?

Researching the background: endometrial biopsy and IVF

- Aust N Z J Obstet Gynaecol. 2009 Dec;49(6):677-80. Endometrial local injury improves the pregnancy rate among recurrent implantation failure patients undergoing in vitro fertilisation/intra cytoplasmic sperminjection: a randomised clinical trial. Karimzadeh MA, Ayazi Rozbahani M, Tabibnejad N.
- Fertil Steril. 2010 Feb 18. Promoting implantation by local injury to the endometrium. Almog B, Shalom-Paz E, Dufort D, Tulandi T.
- Local injury of the endometrium induces an inflammatory response that promotes successful implantation. Gnainsky Y, Granot I, Aldo PB, Barash A, Or Y, Schechtman E, Mor G, Dekel N.

Summary

- Why bother doing research at all?
  - Its gratifying and useful
- What's worth studying?
  - Hugely important - work with a team
- How to define your question?
  - PICO; make sure explicit and feasible
- Matching study architecture to the question
  - Choose least biased option
- Researching the "background"
  - Depends of level of need


BRITISH
Identity Card Issued
COCHRANE
Archibald Lawrence

Quality is everything…

- “I have given up my attempt to change the world as I once wanted to….I feel that I should just concentrate on changing a small bit of it. It’s a bit more effective if one does it that way”

*Archie Cochrane**