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# Problems, solutions and challenges using routinely collected data in a randomized controlled trial setting

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## Explanatory Trials:

- Typical trials examine the effectiveness of a new treatment or an existing treatment for a new indication
- These trials include:
  - Carefully selected patients
  - Detailed follow-up of patients (eg. lab tests, compliance)
  - Support that goes beyond normal clinical care

Explanatory Trials:

- Usually have clearly defined regular study visits throughout the study
- Study data are collected at each visit using a study case report form
- Data issues/problems are queried and updated/corrected

## Pragmatic Trials:

- Trial should reflect routine care
- Naturalistic setting of treatment
- Minimal additional study requirements after randomization

- Less stringent selection criteria helps recruit patients representing a usual care population
- Patients still randomized to treatment to avoid bias. However these trials are commonly not blinded to allocated treatment.

## Pragmatic Trials:

- Study outcome data are retrieved remotely where possible
- Electronic Health Records (EHR) provide a potential solution
  - Data available have to be accepted as is
  - No option to query data
- Study medication is prescribed and collected as in usual practice

## Benefits and Weaknesses:

### Data accuracy and completeness:

- Explanatory Trial:
  - Great attention to detail, querying and monitoring
  - Data collection standardised across sites
- Pragmatic Trial:
  - Subject to the standards of the EHR
  - Data of interest may not be available in the EHR (eg PROMs)
  - Potential for differing systems across sites

## Benefits and Weaknesses:

### Financial Costs:

- Explanatory Trial:
  - Can be very expensive – costs required for each patient attending each scheduled visit and treatment of interest

- Pragmatic Trial:
  - A much cheaper alternative – can reduce the need for patients attending follow-up visits entirely, so the main costs are recruitment and the treatment of interest

## Benefits and Weaknesses:

### Generalizability:

- Explanatory Trial:
  - Generalizable limited to  types of patients recruited with the level of support provided in the trial

- Pragmatic Trial:
  - More generalizable to routine clinical practice

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# The Standard care versus Celecoxib Outcome Trial

# (SCOT)

MacDonald TM et al (2013) “Methodology of a large prospective, randomised, open, blinded endpoint streamlined safety study of celecoxib versus traditional non-steroidal anti-inflammatory drugs in patients with osteoarthritis or rheumatoid arthritis: protocol of the standard care versus celecoxib outcome trial (SCOT)” *BMJ Open*, 2013(3) e002295.

The University of Nottingham

## Background:

- Overall risk/benefit balance of Celecoxib (COX-2) vs. non-selective Non Steroidal Anti-Inflammatory Drugs (NSAIDs) is unknown

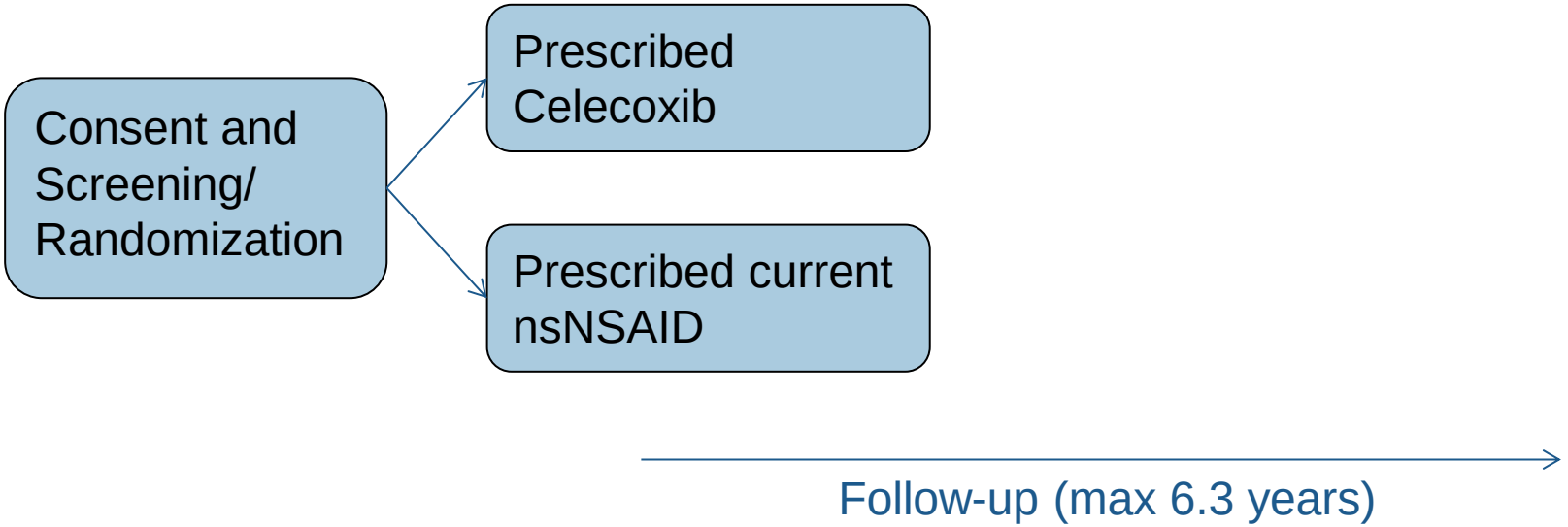
- Primary Objective – Compare the cardiovascular safety of Celecoxib and nsNSAIDs in patients currently using nsNSAIDS for OA or RA

## Background:

- Primary Endpoint – hospitalization for non-fatal myocardial infarction, or other biomarker positive acute coronary syndrome, non-fatal stroke or CV death

- 7,297 patients recruited and randomized from primary care practices in Scotland, Denmark, England and the Netherlands

## Study Design:



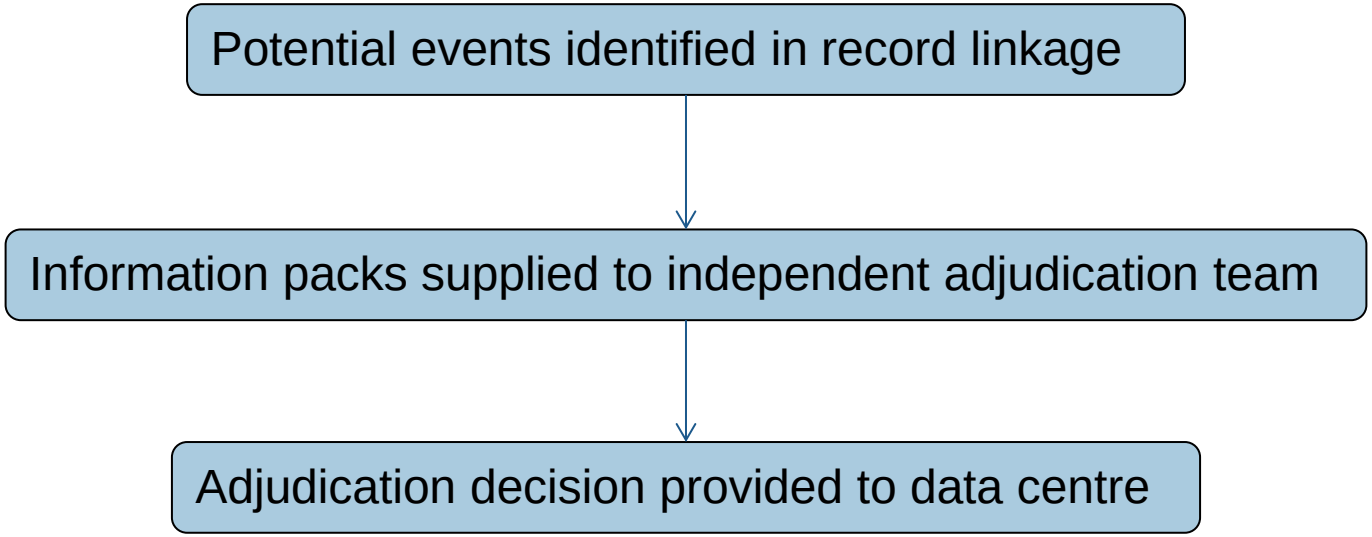

- Prospective, Randomized, Open label, Blinded Endpoint evaluation

## Anticipated Advantages:

- Full collection of serious adverse events and outcomes

- Complete treatment dispensing information available

## Endpoints:


Potential events identified in record linkage
Information packs supplied to independent adjudication team
Adjudication decision provided to data centre

# Challenge 1 – Record Linkage data available

| Problem | Solution |
|---|---|
| **Some countries had different rules of access to record linkage, or changed the rules of access to record linkages during the study** | Check each countries data availability at the start and if it is noted that a change to the rules has been made, try to address this at the earliest opportunity |
| **Differences in coding across countries – additional workload** | Ensure data are obtained in a timely fashion and any codes required for the identification of specific events are available |

# Challenge 2 - Prescription data available

| Problem | Solution |
|---|---|
| **Scotland changed from a single national primary care system to multiple commercial systems with data access limitations** | Introduction of national integrated dispensing database |
| **Different levels of information available across countries** | Identify minimal data available across all countries<br>Is this a solution? |
| **Differences in coding across countries – additional workload (same problem as with events via record linkage)** | Ensure data are obtained in a timely fashion and any codes required for the identification of medications of interest are available |

# Challenge 3 – Changes to medication guidance

| Problem | Solution |
|---|---|
| **Guidance on use of diclofenac changed during the trial** | Review and update protocol and planned analysis to include an analysis allowing patients originally allocated an nsNSAID to swap to other nsNSAIDs |

## Implications and Conclusions:

- Be prepared for the unexpected when using routinely collected data
- Design the study around data availability
- Understand the data you are going to get before the study starts – don’t believe everything you are told, ask for evidence

## Implications and Conclusions:

- Be prepared for changes to information governance requirements during the study

- Data problems may lead to changes to study design

# Thank you