WP6: Methodological guidance on the analysis and interpretation of non-randomised studies to inform health economic evaluation

IMPACT HTA – 2nd RTD Meeting

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Agenda

- Work-package 6 rationale and objectives
- WP6 research progress, overview and methods:
  - Meta-epidemiological review
  - Workshops
  - Case studies
- Timeline

WP6: Methodological guidance on the analysis and interpretation of non-randomised studies to inform health economic evaluation

WP co-leaders	WP partners
▪ NICE (UK) ▪ LSE (UK)	▪ AOTMiT (Poland) ▪ EASP (Spain) ▪ TLV (Sweden) ▪ UCLM (Spain) ▪ UCSC (Italy)

Background: rationale

- HTA bodies increasingly encounter situations where **no evidence from RCTs is available** and decisions about routine use of new technologies need to be made **based on non-randomised studies**

- There are **additional challenges to the use of non-randomised data** compared to guidance directly informed by RCT evidence. Changes to NICE methods and processes may help improve the way in which such data is incorporated into NICE guidance [1]

- **Empirically grounded recommendations** on the use and interpretation of evidence from non-randomised studies against the background of **novel analytical methods** (e.g., propensity score methods, instrumental variables, and others) are needed

Sources: [1] Bell et al. 2016

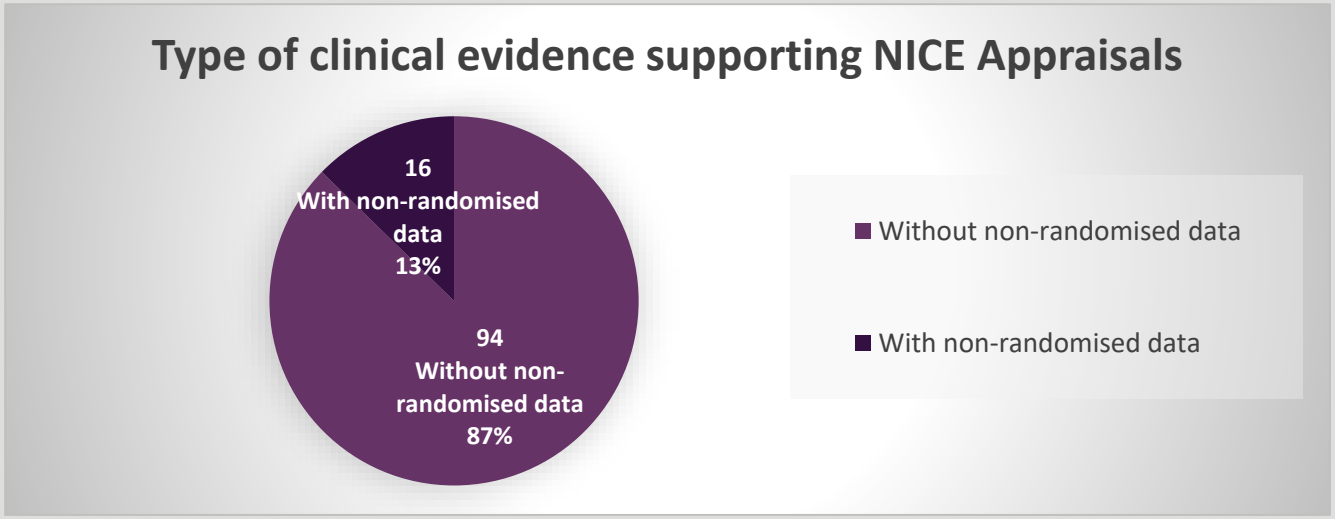
Background: rationale

Reliance of regulatory bodies on non-randomised data

EMA approved cancer drugs from 2009 to 2013	
Total drugs approved	48 for 68 indications
Approved on the basis of a single arm study	8 indications (12%)

From [2]

Reliance of HTA bodies on non-randomised data



From [3]

Sources: [2] Davis et al. 2017; [3] Faria et al. 2015

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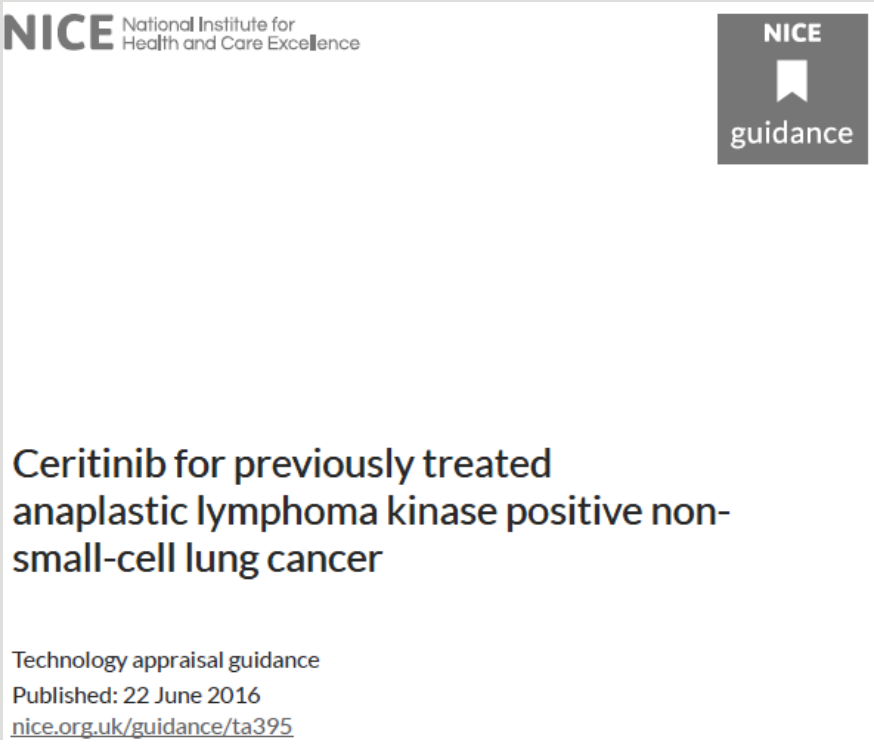
Background: Example of non-randomised evidence in NICE guidance

- Only non-randomised evidence available to inform this appraisal
- Data: 2 single-arm studies of ceritinib; 1 retrospective analysis of overall survival in patients with best supportive care
- Company did indirect comparison of ceritinib with best supportive care, meaning the comparison was not adjusted for differences in patient or study characteristics between studies
- The appraisal committee concluded that ceritinib was likely to prolong life compared with best supportive care, but the extent of treatment benefit was highly uncertain because there was a high risk of bias from confounding



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Aims of WP6

- Generate and write **recommendations** that help health technology assessment (HTA) agencies, regulators and the wider research community to **analyse and interpret non-randomised data** in assessments of relative effectiveness (a key input to economic evaluations)

- Investigate the **extent to which the findings of randomised and non-randomised studies differ** when conducted for the same clinical question and explore potential reasons for observed discrepancies, in particular choice of analytical method

- Assess whether different **analytical methods** used in non-randomised studies are likely to produce **valid and unbiased estimates** of relative effectiveness (a key input to economic evaluations)

- Develop **evidence-based recommendations** for analysing and interpreting non-randomised data in economic evaluations

Three work streams:

Meta-epidemiological review	**Workshops**	**Case studies**
Obtain **empirical estimates** of discrepancy in treatment effects between **matched randomised and non-randomised studies**	Obtain **input on stakeholder needs** and **ensure relevance** of recommendations	**Test relevance and applicability** of draft recommendations in the real world
Preliminary findings: Q3 2019 Final report: Jan 2020	First workshop: Nov 2018 Second workshop: Q1/2 2020	Q3/4 of 2019

We organised a workshop

1) to raise awareness of the work we are doing in WP6 of IMPACT HTA amongst a specialist audience;

2) to give potential users of our outputs the opportunity to steer us to make them as easily adoptable as possible;

3) to identify gaps not addressed by WP6 that would be important to address in the future

Key lessons from the workshop

- There is a general wish for consensus around the situations where RCT evidence would be mandatory and when reliance on non-randomised evidence would be acceptable
- HTA agencies have appetite for guidance on the strengths and weaknesses of methods used to adjust biases of non-randomised data;
- Attendees recommended that we keep an open mind regarding the possible outcomes of this research: what if we found that non-randomised data is much closer to real-world practice than RCTs?;
- A policy relevant consideration to understand differences in how countries might approach the use of non-randomised data in their decisions is that some systems will not do re-assessments of the evidence and will not do coverage with evidence development.

Overview of empirical work

- *How do treatment effects obtained from randomised vs. non-randomised studies for the same intervention in similar populations compare overall and when using different analytical methods?*
- *Which analytical method yields effect sizes that are most similar to those obtained from randomised studies?*

- Large-scale **meta-epidemiological review** [4-7] of studies of pharmacological interventions
- Identify **clinical topics** with randomised and non-randomised studies answering the same clinical question in comparable populations
- **Two-stage meta-analysis** to obtain pooled estimates of discrepancies in treatment effects
- Evaluate **performance** of **different analytical methods**

Sources: [4] Sterne et al. 2002
[5] Schulz et al. 1995
[6] Wood et al. 2008
[7] Ioannidis et al. 2001

Meta-epidemiological review

- Protocol for the meta-epidemiological review was registered on PROSPERO: CRD42018062204
  - Search strategy
  - Data to be extracted
  - Methods for analysis, including sensitivity analyses [4, 7-9]
- Presented to academics, HTA bodies and regulators at workshop in Nov 2018

PROSPERO International prospective register of systematic reviews

NHS National Institute for Health Research

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Comparison of treatment effects in randomised vs. non-randomised studies and the role of analytical methods to control for confounding: a meta-epidemiological study

Maximilian Salcher-Konrad

Citation

Maximilian Salcher-Konrad. Comparison of treatment effects in randomised vs. non-randomised studies and the role of analytical methods to control for confounding: a meta-epidemiological study. PROSPERO 2018 CRD42018062204 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018062204

Review question

In this study, we are interested in how 1) randomisation and 2) different analytical methods used in non-randomised studies impact on treatment effects. The specific research questions we aim to answer are the following:
- How do treatment effects obtained from randomised vs. non-randomised studies for the same pharmaceutical intervention in similar populations compare overall?
- How do treatment effects obtained from randomised vs. non-randomised studies for the same pharmaceutical intervention in similar populations compare when using different methods for the analysis of non-randomised studies?
- Which analytical method yields effect sizes that are most similar to those obtained from randomised studies?

Searches

We aim to identify a set of clinical topics covering a broad range of pharmaceutical interventions and therapeutic areas, and for which both randomised and non-randomised studies exist, through the following steps:
a. Identify clinical topics through previous meta-epidemiological reviews and recent meta-analyses from MEDLINE and the Cochrane Database of Systematic Reviews that included randomised controlled trials (RCTs) and non-randomised studies:
a.1. We will review previous meta-epidemiological reviews that analysed treatment effects in RCTs and non-randomised studies for the same clinical topic. We are aware of a number of such studies. In addition, we will update the MEDLINE (via PubMed) search of an umbrella review published in 2014 (Anglemyer, Horvath and Bero, 2014) to identify any subsequently published meta-epidemiological studies.
a.2. We will search MEDLINE (via PubMed) for meta-analyses that included both RCTs and non-randomised

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Sources: [4] Sterne et al. 2002
[7] Ioannidis et al. 2001
[8] Deeks et al. 2003
[9] MacLehose et al. 2000

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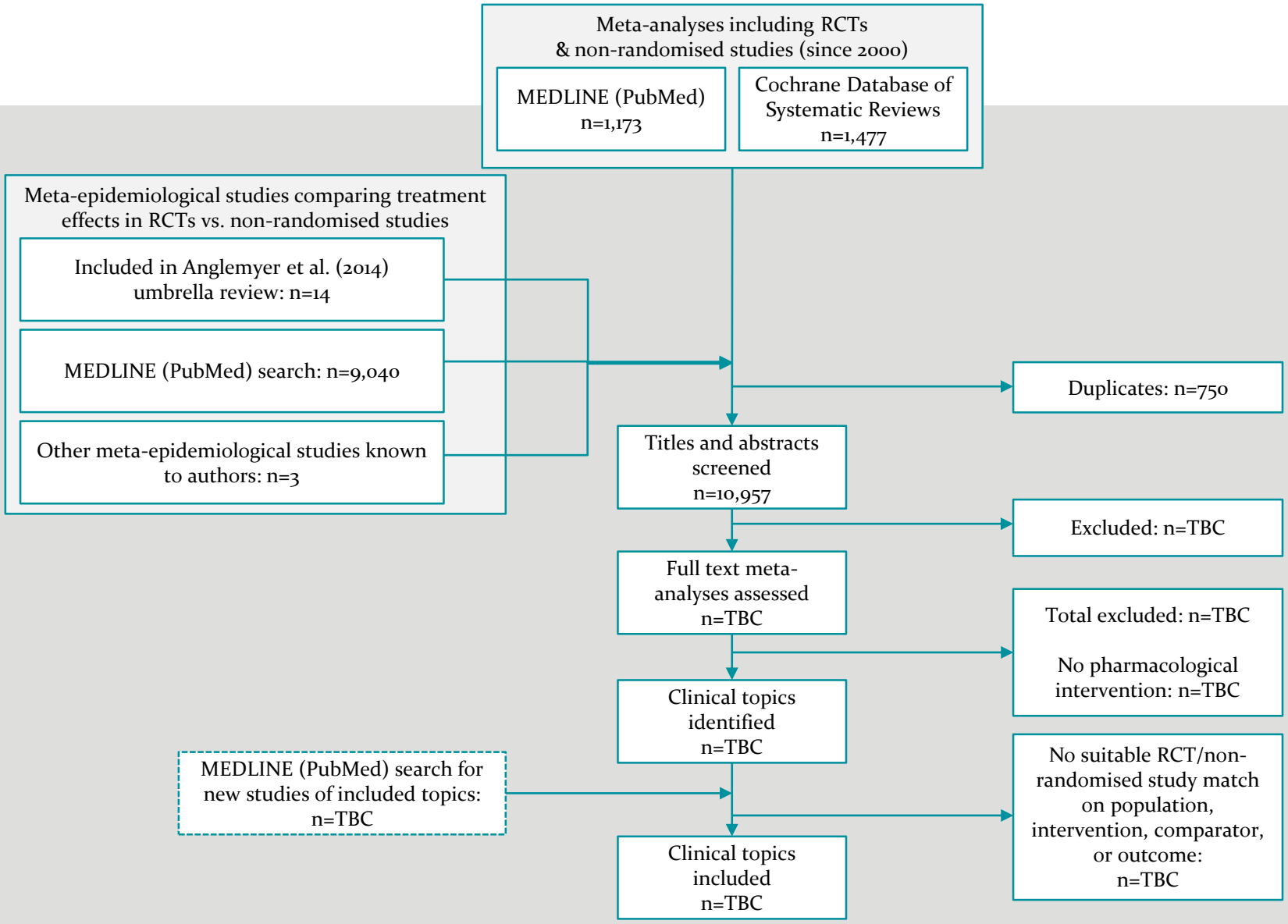
Meta-epidemiological review



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Examples of clinical topics

- >40 topics identified from previous reviews
- Some examples:
  - Long-term mortality after statins in non-ST-elevation acute coronary syndrome
  - Survival after first-line pazopanib for metastatic renal cell carcinoma
  - 6-minute walking distance after bosentan for chronic thromboembolic pulmonary hypertension
  - Depression score after fluoxetine vs. venlafaxine for major depressive disorder
  - Preoperative aspirin and bleeding in patients undergoing elective coronary artery bypass grafting surgery
  - Carvedilol for prevention of atrial fibrillation after cardiac surgery
  - Oral antithrombotics for stroke prevention in atrial fibrillation
  - Anticoagulant vs. antiplatelet therapy and major extracranial bleed in patients with acute ischemic stroke
  - Low/medium/high exposure to non-steroidal anti-inflammatory drugs and pancreatic cancer risk
  - Statins and breast/prostate/colorectal/lung/gastric cancer

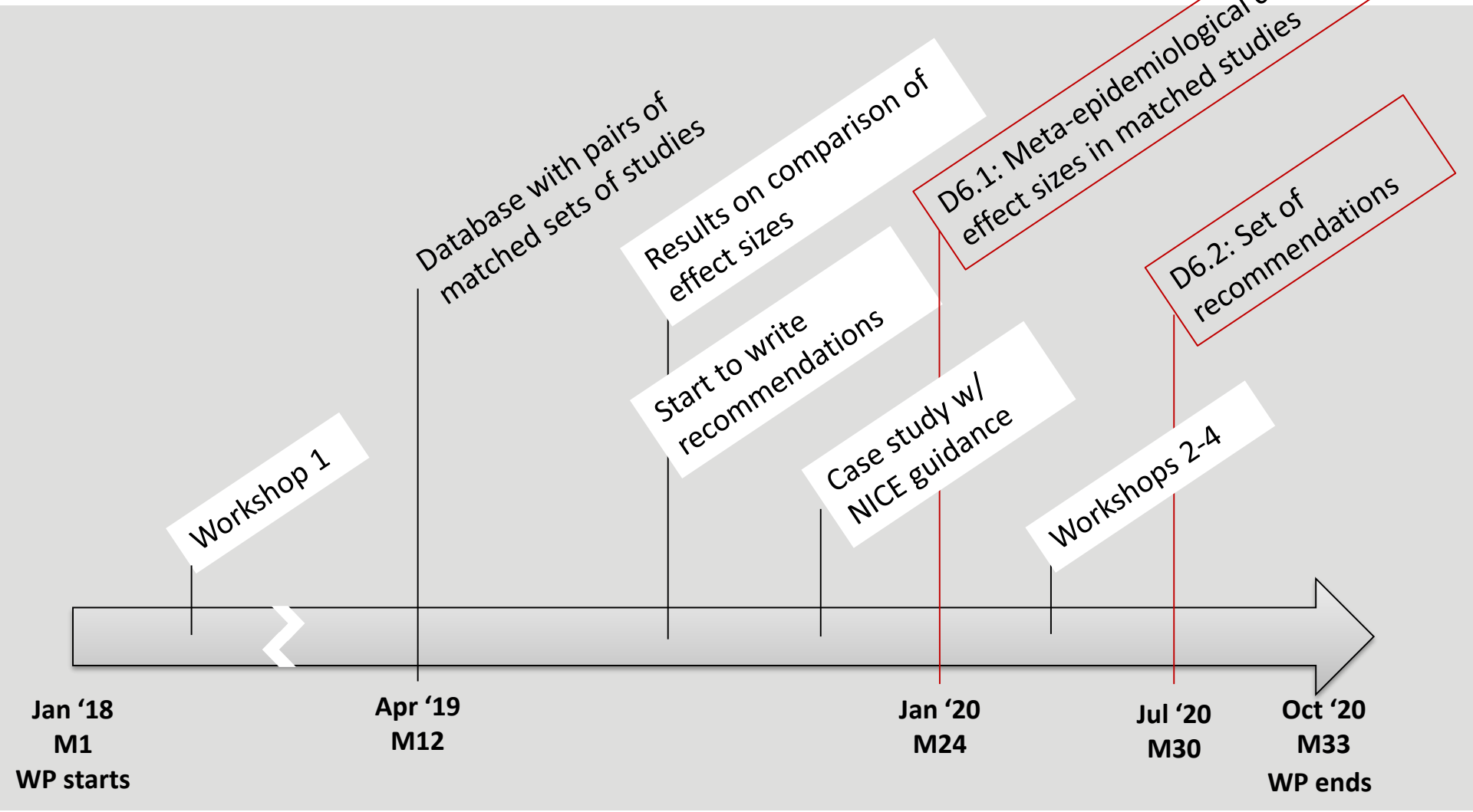
Case study

- We will apply the recommendations to published guidance
  - Confirmed case study with NICE guidance; possible additional case studies in other countries
- Showing how the recommendations are used to analyse and interpret non-randomised data in practice will illustrate the usefulness of the recommendations
- We will apply the recommendations to the clinical evidence that supported the appraisal of ponatinib:
  - The clinical evidence came from a phase II, single-arm, open-label, non-comparative study
  - The company used matching adjusted indirect comparison to compare ponatinib with bosutinib

WP deliverables: 2 publications planned

- Report on the findings of the meta-epidemiological review
  - Deliverable due in January 2020
- Set of empirically grounded recommendations on the analysis and interpretation of non-randomised studies for health economic evaluation
  - Deliverable due in July 2020

Timeline



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Concluding remarks

- Ambitious project that aims to improve our understanding of **risk of bias associated with non-randomised studies** at a time when **'real world' data & advanced methods for analysis** are increasingly available
- **Most comprehensive** meta-epidemiological review since 2001; **first** to consider a range of analytical methods used in non-randomised studies
- **Practice-relevant research** that will lead to recommendations for those using non-randomised studies for decision-making

Questions?

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