OHDSI-EHDEN Studyathon

Edward Burn and James Weaver

OHDSI Community Call

19 February 2019

Agenda

I. OHDSI-EHDEN Studyathon
II. Background
III. Methods
IV. Results
V. Discussion

I. OHDSI-EHDEN Studyathon

Studyathon context and working modality

- Led and hosted by the Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford
- December 10th – December 14th, 2018
  - Participating member of EDHEN
  - Approximately 30 multidisciplinary researchers attended
- Purpose:
  - What can a 30-person collaboration accomplish in 5 days using the OHDSI tools and a network of observational databases converted to the OMOP CDM?
  - Ask a research question then design and execute a prediction study and an estimation study

Studyathon context and working modality

- Program
  - Advance: Submit and vote on prediction and estimation questions
  - Day 1: Study design – T, C, & O
  - Day 2: Cohort characterization
  - Day 3: Patient-level prediction
  - Day 4: Population-level effect estimation
  - Day 5: Writing and wrap up
- This presentation reports on the population-level effect estimation study

Studyathon experience

- My background
  - Health economics and epidemiology
  - Using routinely collected data
  - Typically work on all aspects of an analysis (data extraction and cleaning, statistical analysis, and summarising the results)
- Studyathon experience
  - Working in a group- exploiting ‘comparative advantage’
  - OHDSI tools
  - OHDSI community

II. Background

Using real-world data to emulate a target trial

Real-world studies no substitute for RCTs in establishing efficacy


Jim West/Science Photo Library

We live in the real world, so it is reasonable to expect that data collected from the real world should help identify effective therapies. Indeed, rapid increases in the availability of registries, electronic health records, and insurance claims, and the ability to access, process, link, and analyse data from these sources at fairly low cost lend support for calls to replace randomised controlled trials (RCTs) with so-called real-world studies to establish the efficacy of a therapy,[1,2] particularly for common serious diseases with abundant, easily collected data such as

confounders cannot be adjusted for because they are either unmeasured or unknown (eg, clinical judgment or uncaptured contraindications). The E value can quantify the vulnerability of an observed relationship to unaccounted for confounders.[8]

The problem of confounding is elegantly eliminated by large-scale RCTs in which the randomisation process effectively balances all confounders (known or unknown), thus creating groups with essentially identical characteristics that differ only according to their allocated

Clinical Epidemiology

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METHODOLOGY

Observational studies of treatment effectiveness: worthwhile or worthless?

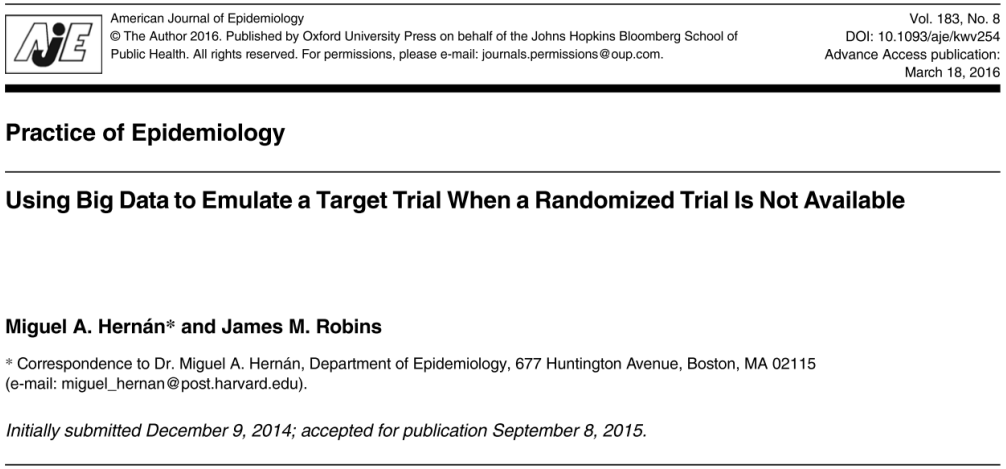
This article was published in the following Dove Press journal:
Clinical Epidemiology

Manuj Sharma[1]
Irwin Nazareth[1]
Irene Petersen[1,2]

Abstract: Observational studies which evaluate effectiveness are often viewed with skepticism owing to the fact that patients are not randomized to treatment, meaning that results are more prone to bias. Therefore, randomized controlled trials remain the gold standard for evaluating

- RCTs remain the 'gold standard' for evaluating treatment effectiveness
- But, RCTs are not always feasible, ethical, or timely
- Even when undertaken, RCTs are often underpowered to assess safety outcomes and heterogeneity in treatment effect

Using real-world data to emulate a target trial



American Journal of Epidemiology
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Vol. 183, No. 8
DOI: 10.1093/aje/kwv254
Advance Access publication: March 18, 2016

Practice of Epidemiology

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

Miguel A. Hernán* and James M. Robins

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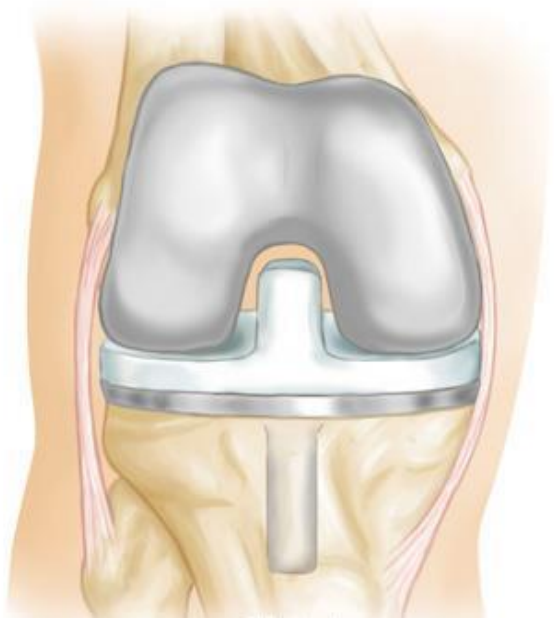
Initially submitted December 9, 2014; accepted for publication September 8, 2015.

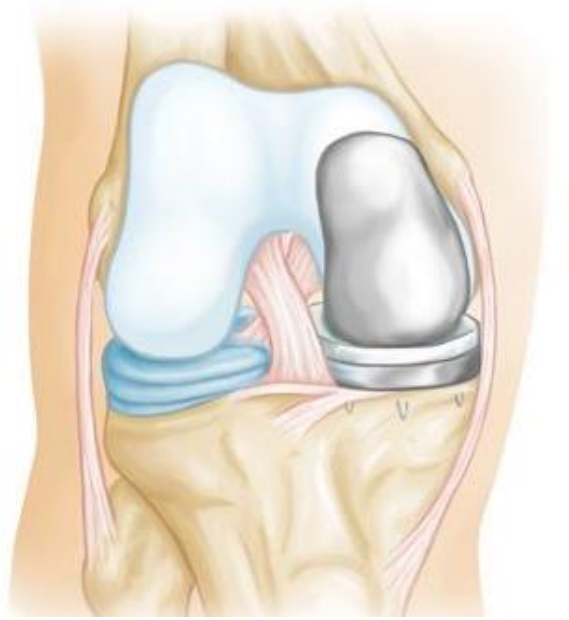
- Observational data can be used to mimic randomized experiments (target trials)
- If emulation is successful, the analysis of the observational data yields the same effect estimates (except for random variability) as the target trial would have yielded

Total knee replacement (TKR)



- For patients with end-stage osteoarthritis, TKR leads to substantial long-term gains in quality of life
- TKR is generally considered cost-effective when compared with non-surgical alternatives

Unicompartmental knee replacement (UKR)



- UKR is an alternative method of knee replacement, where only the affected compartment is replaced
- Up to 50% of patients are eligible for either TKR or UKR
- 8% of knee replacements in the UK are UKR

TOPKAT

Beard *et al. Trials* 2013, **14**:292
http://www.trialsjournal.com/content/14/1/292

TRIALS

STUDY PROTOCOL Open Access

Total or Partial Knee Arthroplasty Trial - TOPKAT: study protocol for a randomised controlled trial

David Beard[1*], Andrew Price[1], Jonathan Cook[3], Ray Fitzpatrick[2], Andrew Carr[1], Marion Campbell[3], Helen Doll[4], Helen Campbell[2], Nigel Arden[1], Cushla Cooper[1], Loretta Davies[1] and David Murray[1]

- 264 patients were randomly assigned UKR with another 264 assigned TKR
- Primary outcome of the trial which is self-reported pain and function, as measured by the Oxford Knee Score
- Secondary outcomes include post-operative complications and rates of revision

Prospective validation of TOPKAT

- In our study we aimed to prospectively emulate the TOPKAT trial using routinely-collected data
- Effect of treatment on
  - Post-operative complications (venous thromboembolism, infection, readmission, and all-cause mortality)
  - Risk of revision
  - Opioid use (as a proxy for post-operative persistent pain)

III. Methods

Network study data sources

Code	Database	Description	Size (M)
CCAE	IBM MarketScan Commercial	US; private-payer claims	138
MDCR	IBM MarketScan Medicare Supplemental	US; private and public-payer claims	10
Optum	Optum Clinformatics DOD	US; private-payer claims	82
THIN	The Health Improvement Network	UK; outpatient EHR	17
PMTX	PharMetrics Plus	US; private-payer claims	130

- UK and US health systems represented

Study design

- Observational, retrospective comparative cohort design
- Key inputs:

Target cohort
Comparator cohort
Outcome cohort
Time-at-risk
Model specification

Study design

- Observational, retrospective comparative cohort design
- Key inputs:

Target cohort	• Unicompartmental knee replacement
Comparator cohort	• Total knee replacement
Outcome cohort	• Venous thromboembolism • Post-operative infection • Readmission • Mortality • Opioid use • Revision
Time-at-risk	• 60 days • 91 days – 365 days • 5 years
Model specification	• 1:10 PS matched conditional Cox PH

Study population - UKR and TKR cohorts

- Cohort entry event (index date)
  - First procedure in person's history
  - At least 1 year prior observation time
- Inclusion criteria
  - At least 40 years old at index
  - No prior knee replacement surgery, revision, or any other knee surgery
  - No prior knee fracture or other knee or knee ligament injuries
  - No prior diagnoses of rheumatoid arthritis or other inflammatory arthropathy
  - No prior septic arthritis
  - No prior back, hip, or foot pain

Outcome ascertainment

- Short-term Post-operative complications
  - Venous thromboembolism
  - Infection at surgical site
  - All-cause readmission
  - All-cause mortality
- Medium-term persistent pain
  - Opioid prescription proxy
- Long-term implant survival
  - Revision procedure
- Primary trial outcome unavailable – self-reported pain and function
- Not all outcomes available in each data source

Time-at-risk periods

- Short-term post-operative complications
- Medium-term persistent pain
- Long-term implant survival

Time-at-risk periods

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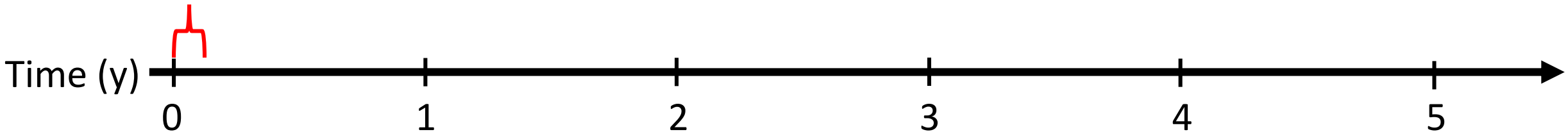
Day 0 – 60



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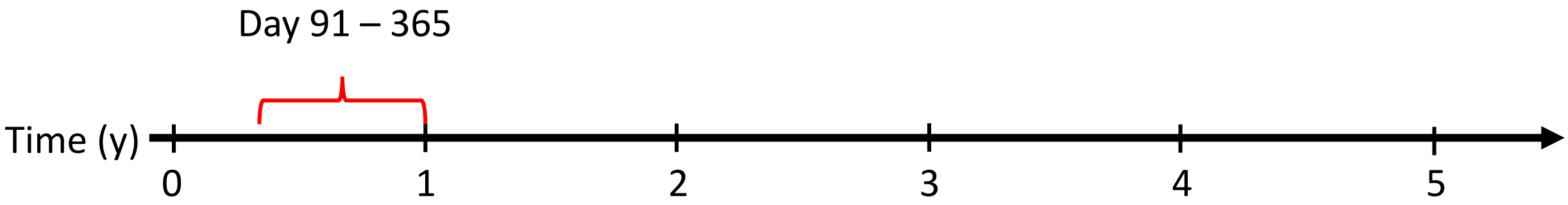

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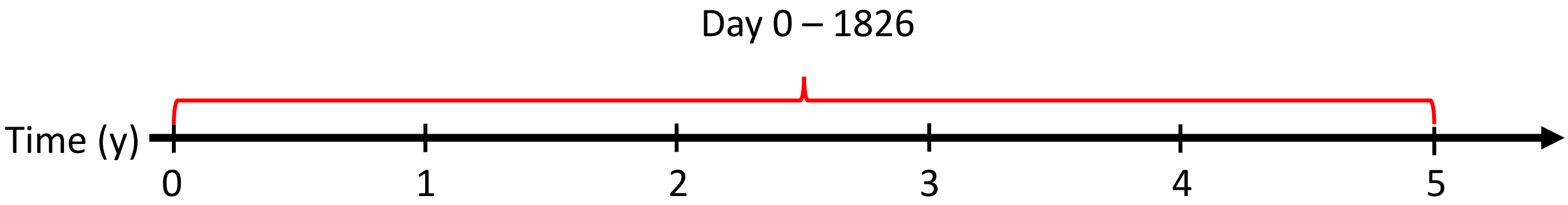


Primary analysis

- 1:10 variable ratio PS matched conditional Cox PH model
- PS model fit with large-scale regularized logistic regression using Laplace prior and optimal hyperparameter selected through 10-fold cross validation

Sensitivity analyses

- Removed no prior pain restriction in cohort definitions
- Extended and reduced time-at-risk periods
- Matched 1:1 on PS
- Trimmed 5% extremes of PS

Diagnostics

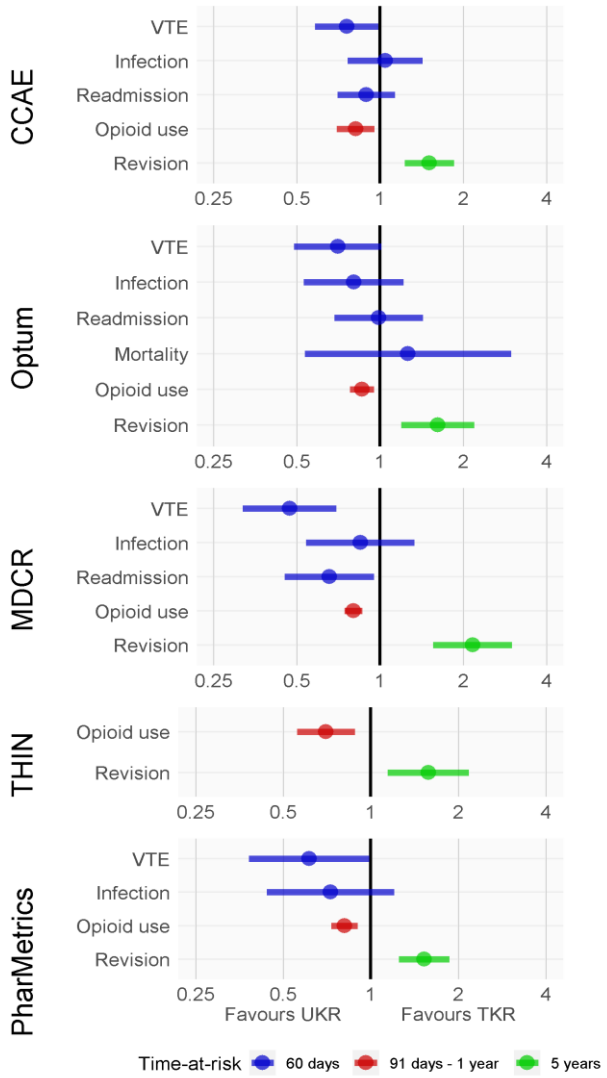
- Preference score overlap
- Covariate balance
- Empirical calibration using 39 negative control outcomes
  - Estimated empirical null distribution to quantify residual random and systematic error
  - Generated synthetic positive control outcomes of known effect sizes to support effect measure and confidence interval calibration
- Outcome model results blinded until diagnostics passed

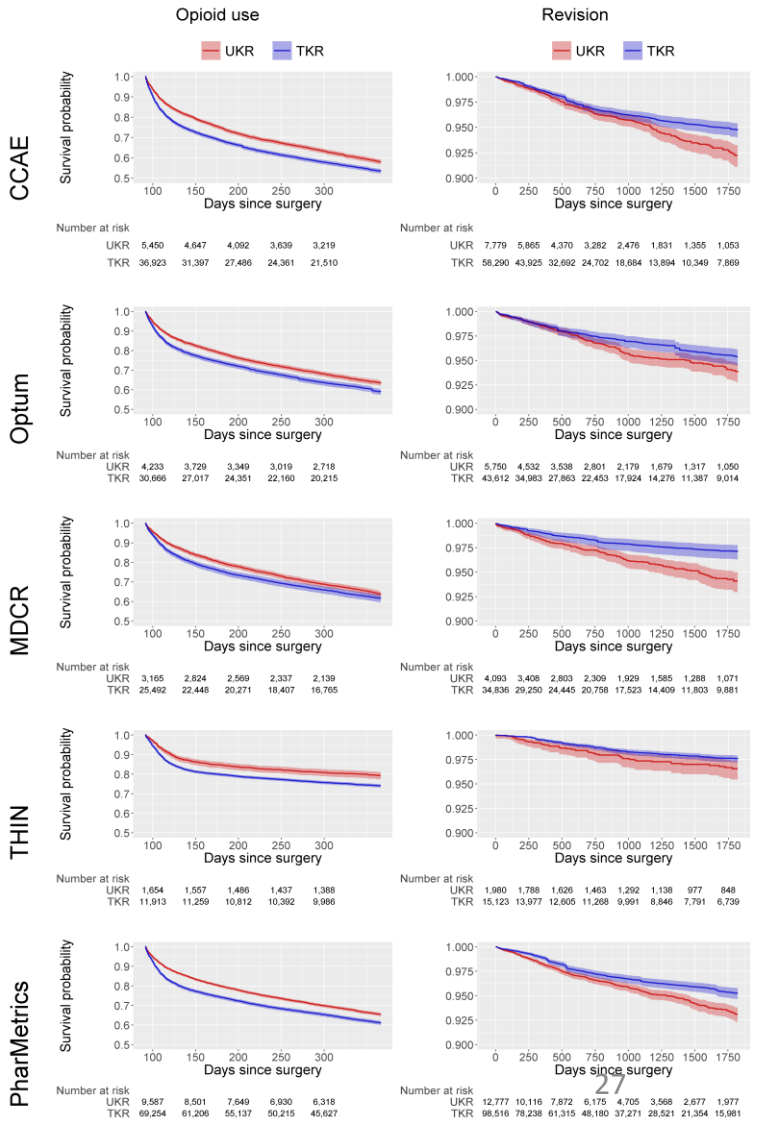
IV. Results

http://data.ohdsi.org/UkaTkaSafetyEffectiveness/

Benefit-risk trade-off for UKR

- Reduced risk for 60 day venous thromboembolism
- Reduced risk 90 day to 1 year opioid use
- Increased risk for 5 year revision
- Consistent across data sources





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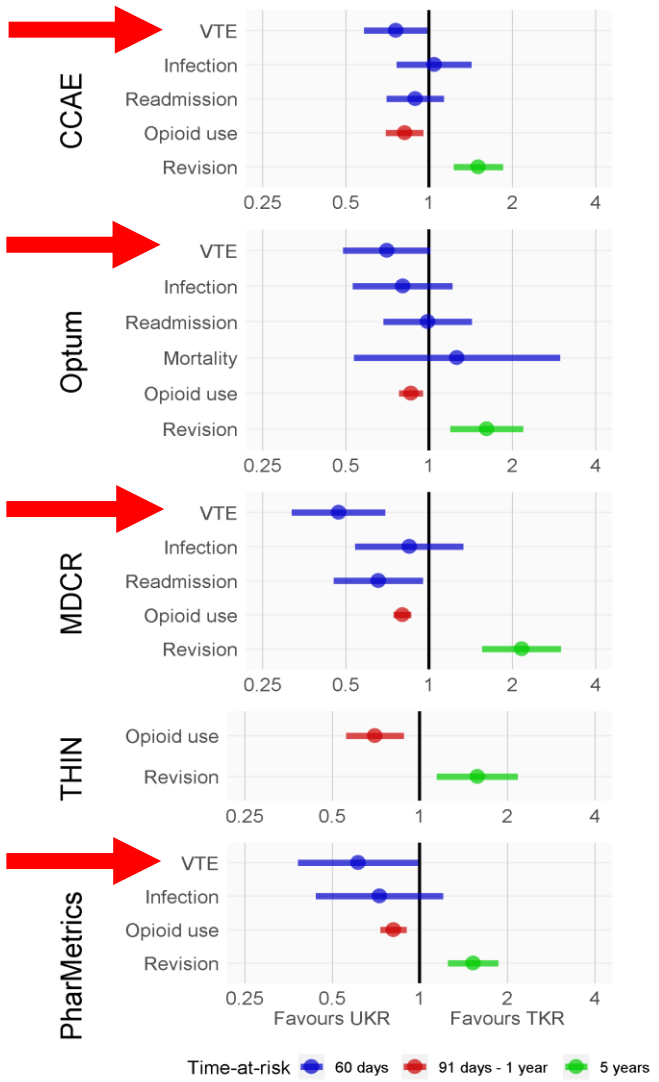

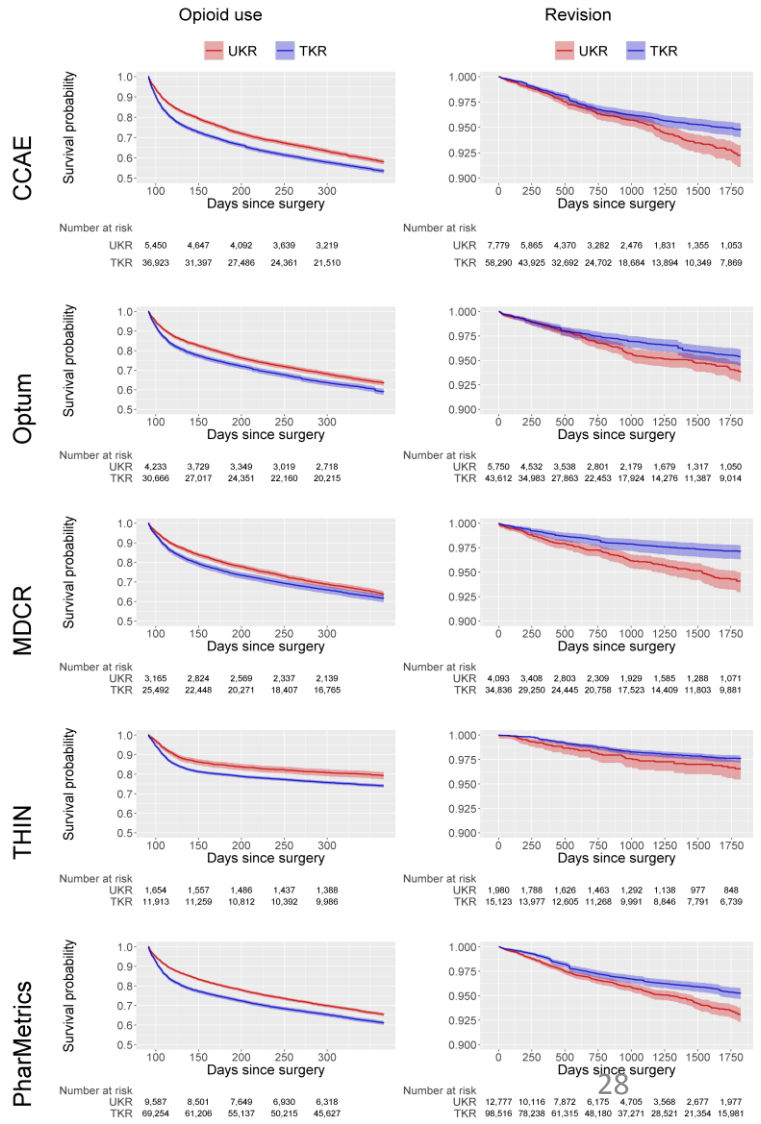

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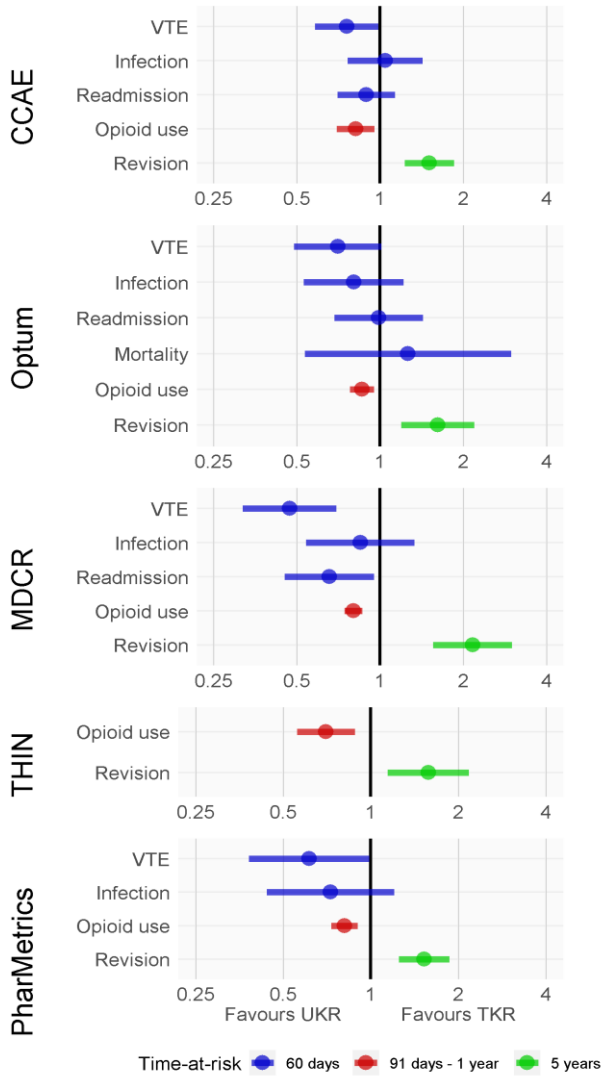

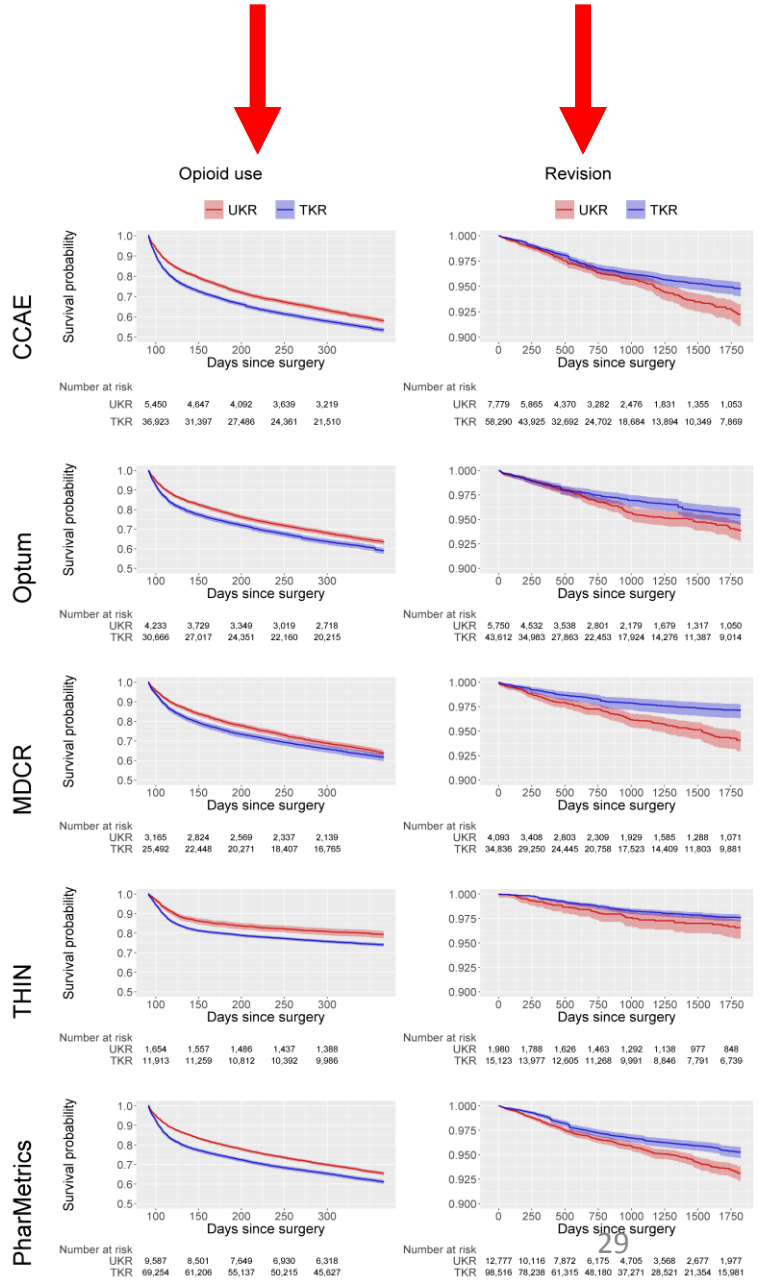

V. Discussion

Clinical results

- UKR was consistently found to have a decreased risk of post-operative venous thromboembolism relative to TKR, but not of other post-operative complications, such as infection and mortality
- UKR was consistently found to result in a lower risk of extended opioid use compared to TKR
- But was consistently found to result in a higher risk of revision compared to TKR

Prediction of TOPKAT findings

- UKR will have a lower rate of venous thromboembolism and a higher rate of revision (HR of around 1.5 to 2). Given sample size, neither difference will likely be statistically significant.
- We cannot directly estimate the effect of procedure on Oxford Knee Score. However, given that we observed consistent reductions in the risk of opioid use for UKR, we can predict that UKR will be associated with better overall patient reported outcomes in TOPKAT.

Implications for future research

- Emulating a target trial using observational data is possible when
  - alternative treatment strategies are being used in routine practice and treatment assignment can be observed,
  - trial eligibility criteria can be observed,
  - confounding can be controlled for, and
  - outcomes of interest (or appropriate proxies) can be observed
- Use of databases converted to OMOP CDM allows for the target trial to be emulated consistently across databases
- OHDSI community and tools allow for research that answers important clinical questions in a robust and timely way

Any questions?

Backup slide 1 – Analysis variants

Target cohort	Comparator cohort	Outcome(s)	Analysis	Time-at-risk	PS matching	Trimming
UKR	TKR	Post-operative complications	Primary	60 days	1:10 variable	None
			Sensitivity	1 year	1:10 variable	None
				5 years	1:10 variable	None
				60 days	1:10 variable	5%
				60 days	1:1	None
		Revision	Primary	5 years	1:10 variable	None
			Sensitivity	1 year	1:10 variable	None
				5 years	1:10 variable	5%
				5 years	1:1	None
		Opioid use	Primary	91 days-1 year	1:10 variable	None
			Sensitivity	91 days-5 years	1:10 variable	None
				91 days-1 year	1:10 variable	5%
				91 days-1 year	1:1	None
UKR without prior pain restriction	TKR without prior pain restriction	Post-operative complications	Sensitivity	60 days	1:10 variable	None
				1 year	1:10 variable	None
				5 years	1:10 variable	None
				60 days	1:10 variable	5%
				60 days	1:1	None
		Revision	Sensitivity	5 years	1:10 variable	None
				1 year	1:10 variable	None
				5 years	1:10 variable	5%
				5 years	1:1	None
		Opioid use	Sensitivity	91 days-1 year	1:10 variable	None
				91 days-5 years	1:10 variable	None
				91 days-1 year	1:10 variable	5%
				91 days-1 year	1:1	None

Backup slide 2 – Negative control outcomes

Acquired hallux malleus

Acquired hallux valgus

Acquired trigger finger

Allergic rhinitis

Astigmatism

Benign neoplasm of colon

Breast lump

Carpal tunnel syndrome

Cataract

Chronic obstructive lung disease

Diaphragmatic hernia

Disorder of brain

Disorder of breast

Disorder of lung

Diverticular disease of colon

Essential hypertension

Gastroesophageal reflux disease with esophagitis

Gastroesophageal reflux disease

Glaucoma

Hand pain

Hyperlipidemia

Hypermetropia

Hypothyroidism

Impacted cerumen

Kidney stone

Menopausal syndrome

Nicotine dependence

Otitis media

Presbyopia

Rosacea

Sleep apnea

Tear film insufficiency

Tinnitus

Type 2 diabetes mellitus

Uncomplicated asthma

Urinary incontinence

Vitamin B deficiency

Vitamin D deficiency

Wrist joint pain

Backup slides 3 – Diagnostics