COMBINING MULTIPLE DATA SOURCES FOR COMPARATIVE EFFECTIVENESS

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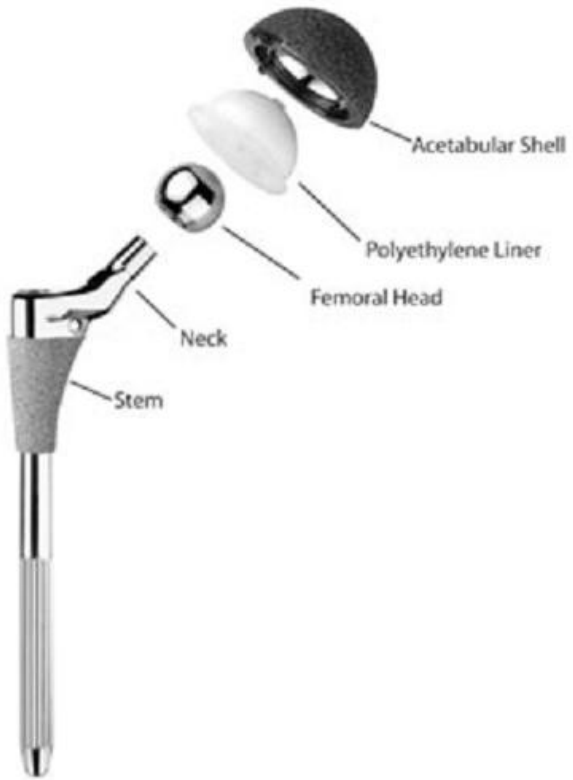
May 7, 2010

MOTIVATION

Cannot efficiently produce **safety and effectiveness information** under current paradigm

1. Technology and innovation evolve **rapidly**
   - Medical devices are getting smaller & smarter; providing more information; and more convenient for the patient.
2. RCTs are **smaller** and increasingly **not generalizable**
   - Representative of about 10% of potential population; multiple illnesses; multiple protocols.
   - Under-powered for low-risk events.
3. Increasing **heterogeneity** among treatment effects when broadening inclusion criteria
4. National coverage decisions for new medical technologies requires the need for **extrapolation** of treatment benefits observed in one population to the nation.

Total Artificial Hip



Context: USA

1. **18.2%** of Americans will be affected by arthritis by 2020
   - **200,000** total hip replacements; **100,000** partial hip replacements; average total cost of **$25,000**
   - Younger patients will account for more than **half** of hip replacements procedures
2. Artificial hips used to treat joint failure
   - **Total** Hip Replacement: Replace head of thigh bone and hip socket with a device
   - **Partial** Hip Replacement: Replace hip socket
   - **Bearing** surfaces can differ across devices

Context: USA

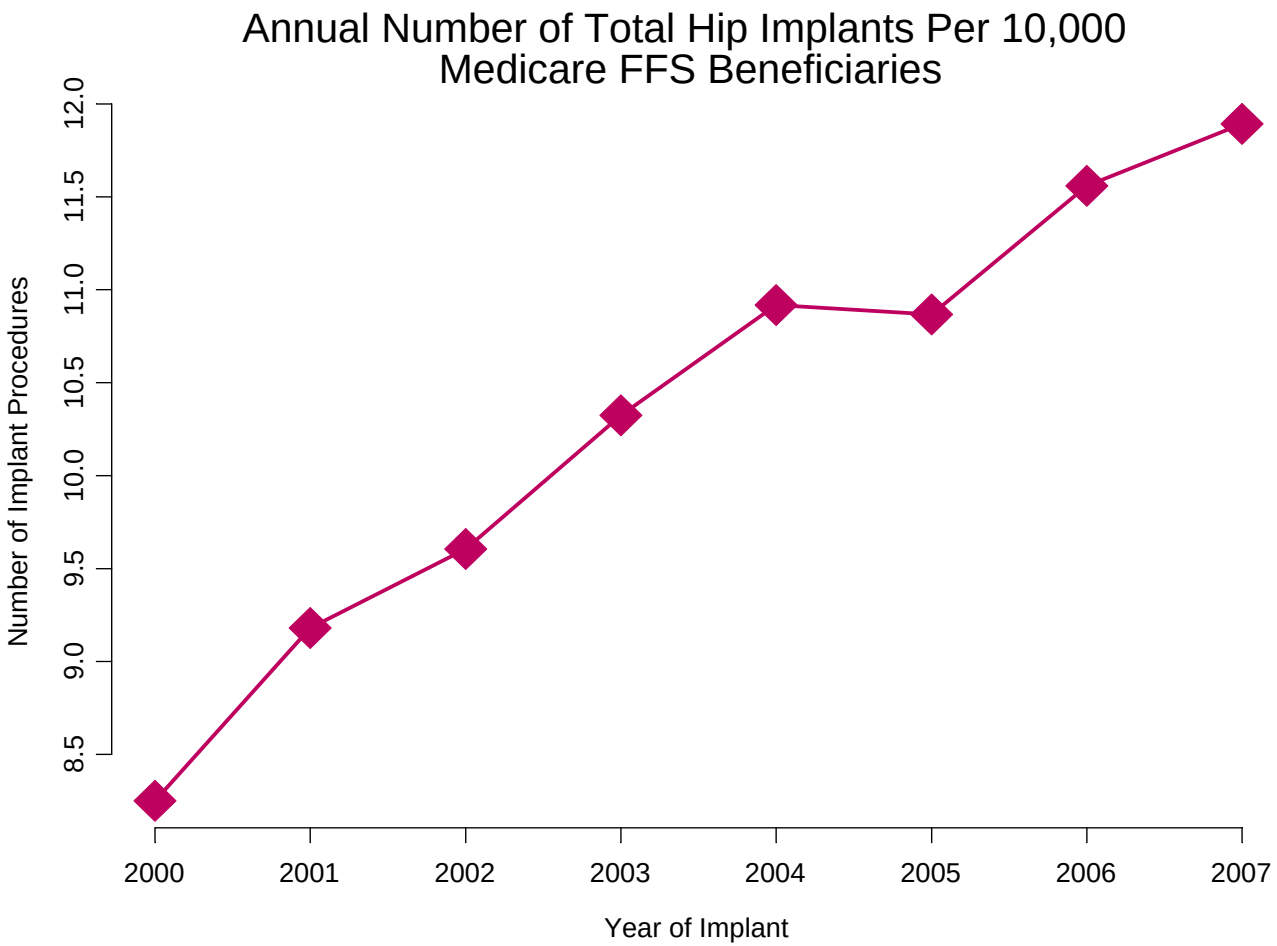
As of June 30, 2009: **10** ceramic-on-ceramic hips approved US

- BUT **half** of these systems were granted approval by a licensing agreement with one company;
- **No new clinical data** were collected.
- No long term outcomes

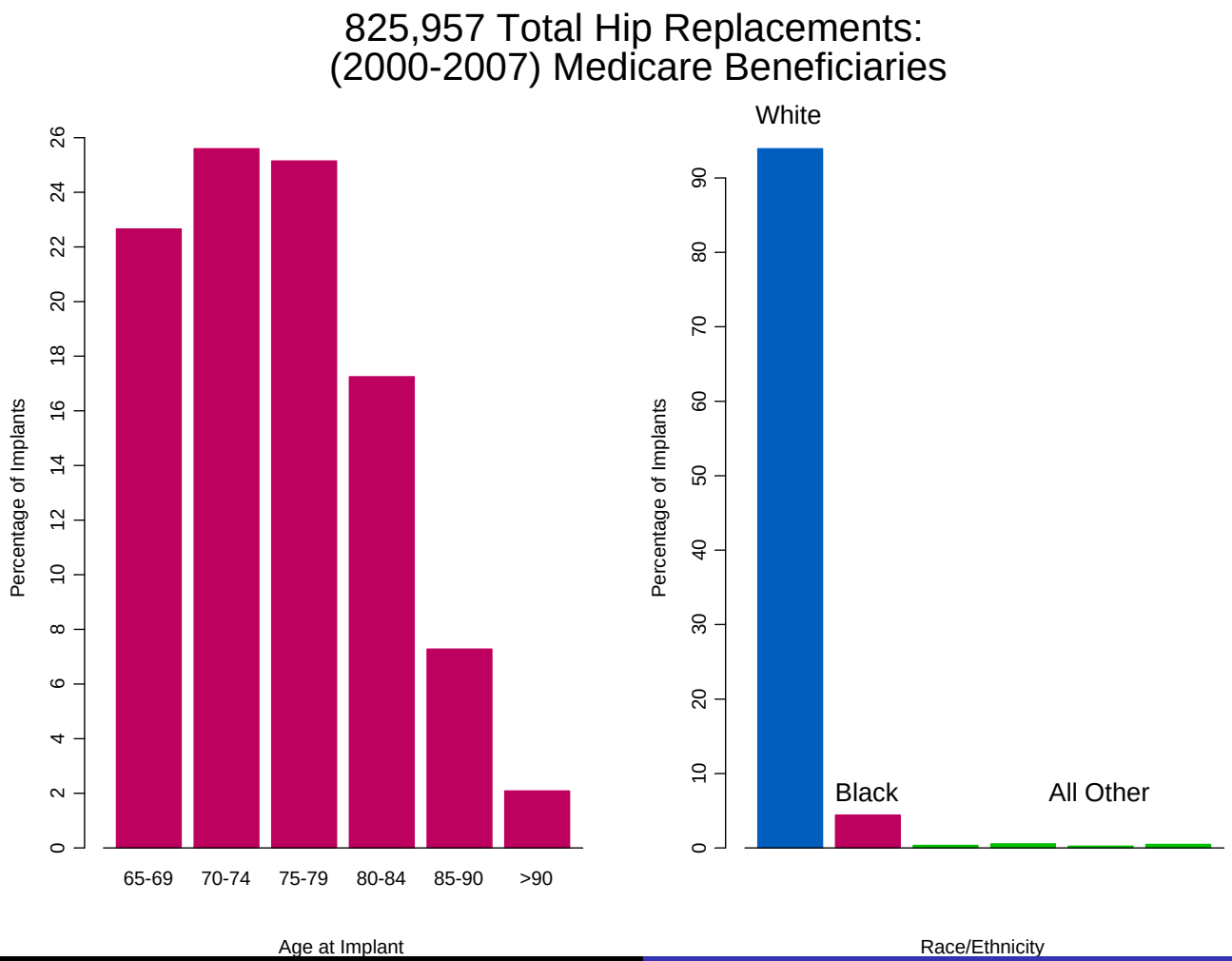
Few, if any, **head-to-head** comparisons within class

HOW EFFECTIVE ARE CERAMIC-ON-CERAMIC ARTIFICIAL HIPS?

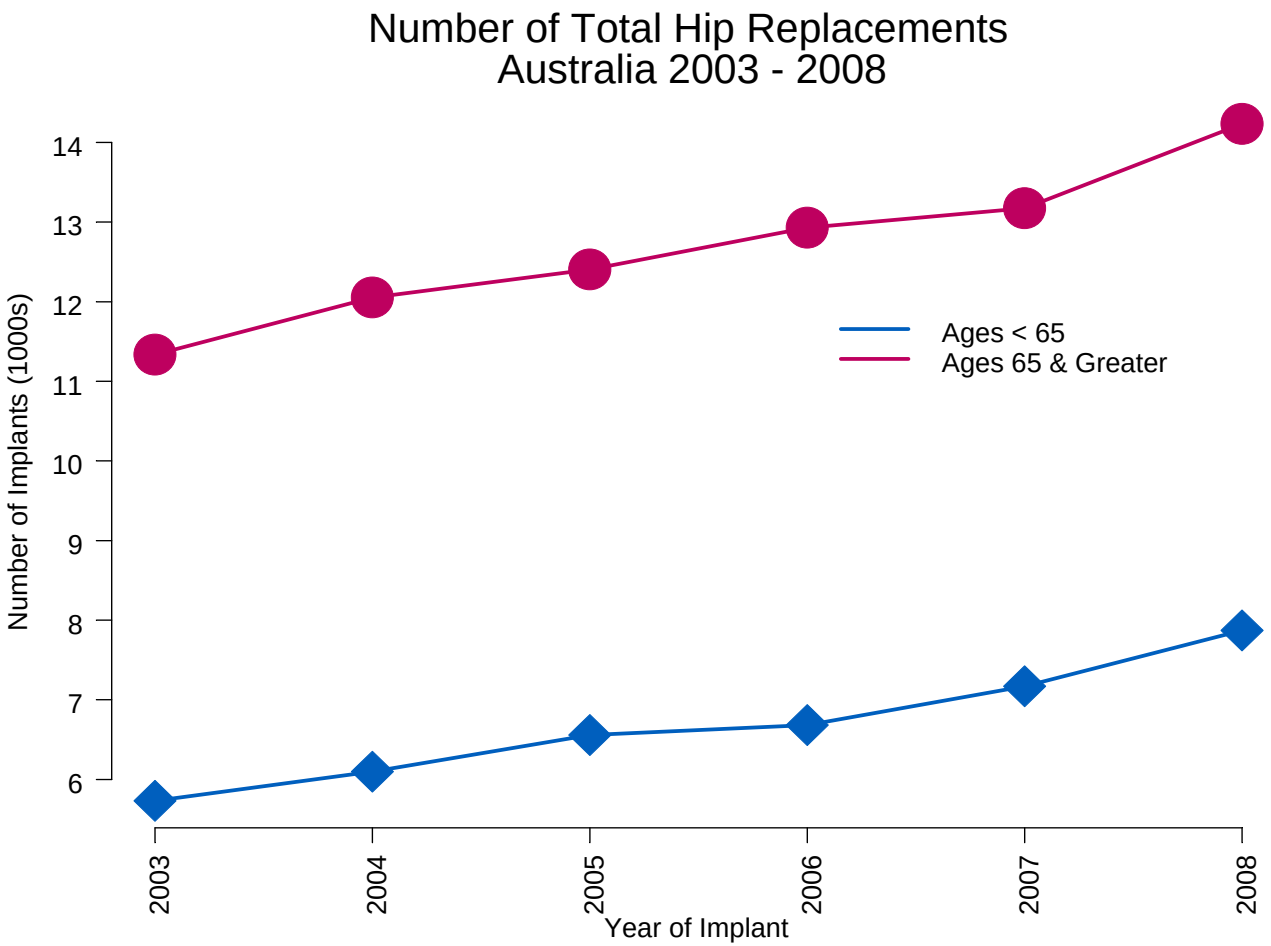
US FFS Medicare Population



US FFS Medicare Population



Outside US Experience



Bearing Surfaces and Outcomes

1. Categories of artificial hips
   - Prior to 1976: metal femoral heads with polyethylene liner in the aceteabular cup (metal-on-plastic)
   - Prior to 1976: metal heads and metal cups (metal-on-metal)
   - 2003: ceramic heads and ceramic cups (ceramic-on-ceramic)
2. Outcomes:
   - **Effectiveness**: pain and function improvement (Harris Hip Score).
   - **Survivorship**: time to hip revision.
   - **Adverse Events**: radiographic evidence of component loosening or breakage or osteolysis; wear; liner dislodgement; infection.

Data Sources

1. **Experimental Data**
   - Pre-clinical data (bench studies)
   - Pivotal clinical trials
2. **Observational Data**
   - FDA-mandated post-approval studies
   - US registries (Health Plan; American Association of Orthopedic Surgeons)
   - Administrative data (Meciare, hospital, Medicaid)
   - Outside US registries (Australia)

Practical Considerations

1. Multiple **outcomes** - single treatment may have different effects on different outcomes
   - Different outcomes are correlated within a subject
   - Different predictors of effect magnitude for different outcomes
   - Not all outcomes are measured in each study
2. Multiple **treatments**
   - Devices: metal-on-metal, ceramic-on-ceramic, metal-on-plastic
   - Drugs: anti-inflammatory, joint supplements, etc.
3. Not all patient **types** have been randomized
4. Multiple **designs**
   - Randomized; observational
   - Practice Patterns: within-US and outside US

Combining Information

How to use **all** the evidence to obtain more precise estimates of safety and effectiveness of particular devices in particular patients?

- Posit an underlying mechanism that generates the observed data
- While some outcomes may be missing, the set of observed outcomes is **connected**

Connectedness: any observed (i,j,k,m) can be reached from any other (i*,j*,k*,m*)

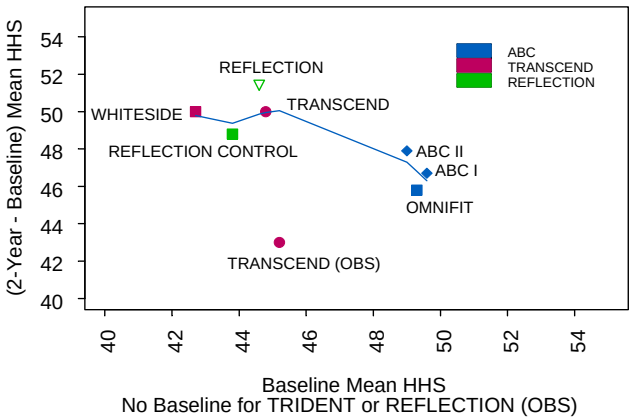
Model	$y_{ijkm} = \alpha_m + \beta_k + \gamma_{mk} + a_i + b_{j(i)} + c_{k(i)} + d_{m(i)} + \epsilon_{ijkm}$
Levels	Study i; Cohort j; Device k; Outcome m
y_{ijkm}	outcome (Mean Harris Hip Score)
α_m	base rate for outcome m
β_k	effect of device k for average study & outcome
γ_{mk}	deviation from average of device k on outcome m
a_i	main effect of study i
$b_{j(i)}$	effect of cohort j within study i on outcome m
$c_{k(i)}$	study-specific effect of device k within study i
$d_{m(i)}$	study-specific effect of outcome m within study i
ϵ_{ijkm}	sampling error of outcome m

	Ceramic-on-Ceramic			Ceramic-on-Polyethyline	
Outcome	ABC 1	ABC 2	Reflect	OMNIFIT	Reflect
BASE HHS	48.3(13) 170	48.7(10.7) 176	44.6(10.7) 174	48.9(12.3) 165	43.8(9.7) 141
2-Year HHS	96.3(8.7) 122	96.9(7.2) 120	95.6(7.5) 139	95.1(6.9) 110	92.1(10.5) 85
Revise Free	139/140	138/140	122/126	128/133	84/85
Outcome	Trident	Transcend Original	 Ext.	Whiteside	
BASE HHS	47.5(11.7) 184	44.8(12.7) 329	45.23(14.7) 639	42.7(11.3) 211	
2-YEAR HHS	? 97	94.8(11) 329	88.1(13.8) 630	92.7(10.2) 211	
Revise Free	?/97	318/329	?/630	207/211	

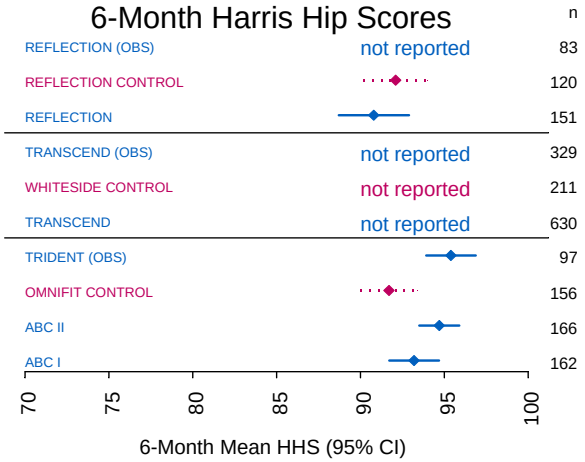
US Pivotal Trial Data

3 Pivotal Studies of 4 Ceramic-on-Ceramic Total Hip Systems

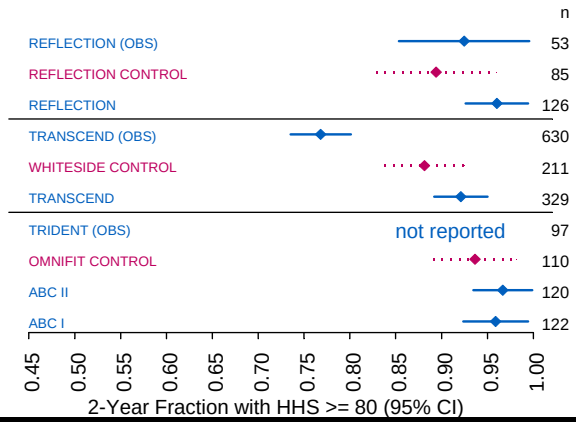
Change in 2-Year HHS by Baseline HHS



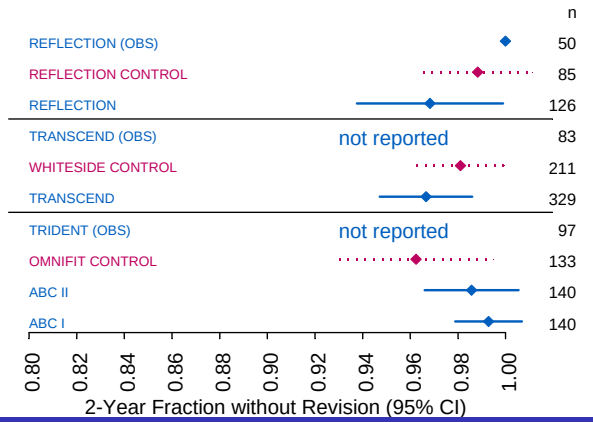
6-Month Harris Hip Scores



2-Year Harris Hip Scores



2-Year Revision Success



Model for Pivotal Trials

- Y_c denotes 2-year **mean** Harris Hip Score
- Y_b denotes **number** of subjects revision-free at 2 years
- σ_{cij} is the **known** standard error of the mean HHS for jth observation from the ith study.

$$
\begin{aligned}
E(Y_{cij}) &= \beta_0^c + \beta_1^c(Ceramic)_{ij} + \beta_2^c(RCT)_{ij} + \sigma_{cij}u_i \quad (1)\\
Y_{bij} &\sim Binomial(p_{ij}, n_{ij})\\
logit(p_{ij}) &= \beta_0^b + \beta_1^b(Ceramic)_{ij} + \beta_2^b(RCT)_{ij} + u_i \quad (2)
\end{aligned}
$$

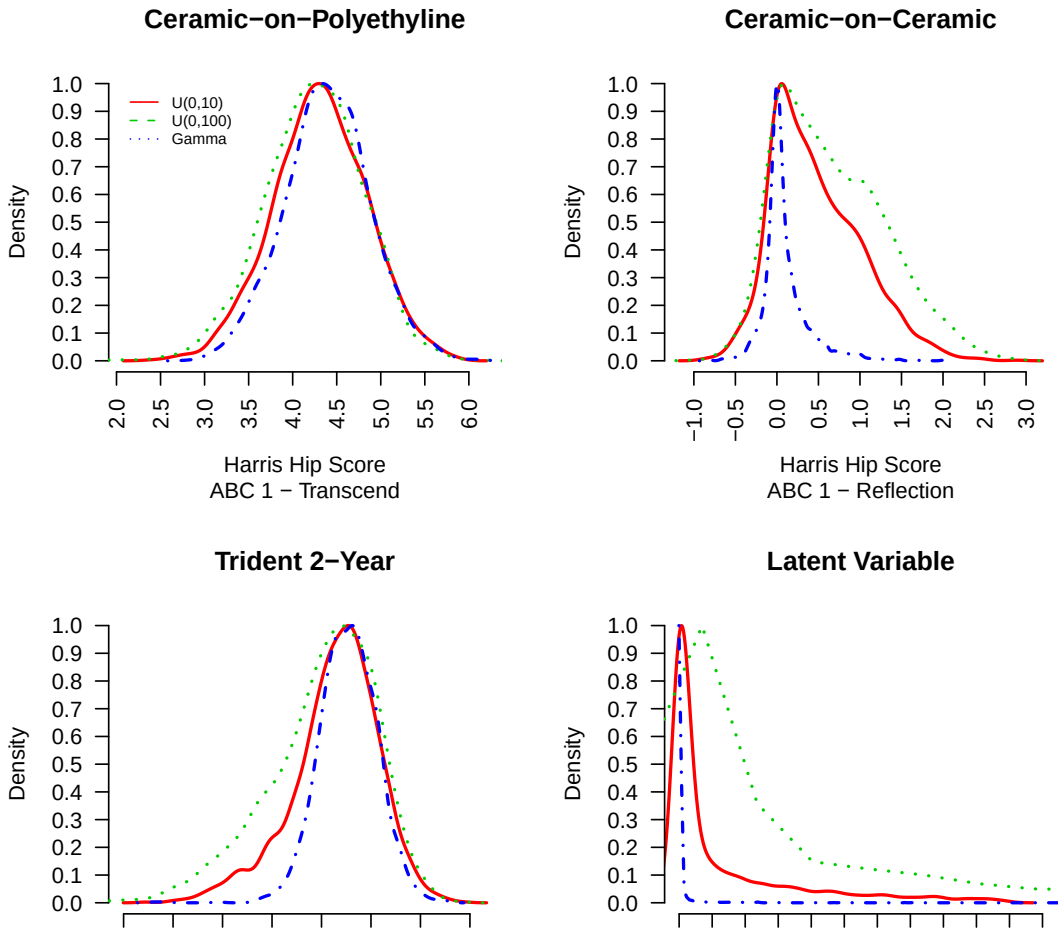
- Assume $u_i \sim N(0, \sigma_u^2)$
- Priors for σ_u^2: $\sigma_u \sim U(0, 10)$; $\sigma_u \sim U(0, 100)$; or $\sigma_u^{-2} \sim$ diffuse gamma

Pivotal Trial Data

Posterior summaries using 3 chains, 12500 burn-in, 2028 used for inference after thinning

	HHS		Revision Success	
Covariate	Mean	SD	Odds Ratio	SD
Intercept	90.6	1.79	33.8	54
Randomized	4.1	0.64	1.14	1.11
Ceramic	-0.002	0.59	1.03	0.46
σ_u^2	PRIOR:	U(0,10)	U(0,100)	Gamma
Mean (SD)		13 (22)	118 (532)	1.69 (15)

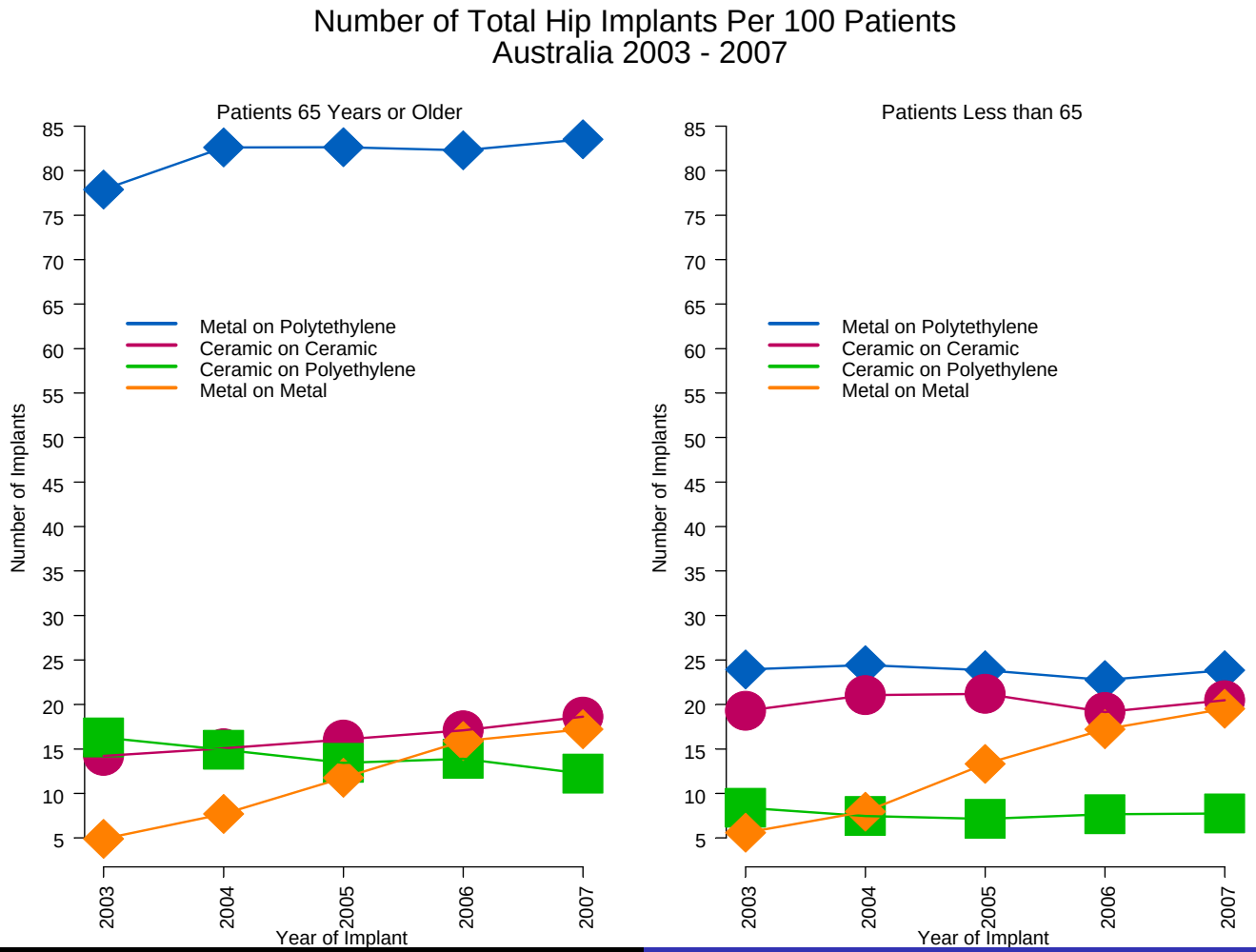
Head-to-Head Comparisons



Going Forward

- Observational studies should form part of the evidence-base for regulatory decisions.
- Need more experience with integrating data from multiple diverse sources in order to inform regulatory decisions.
- Meta-analyses are a good source of information but they are observational studies **and** limited in generalizability of patient and physician population.
- Sensitivity analyses should supplement all analyses (RCT, meta-analyses, observational studies).
- How to assess exchangeability assumptions?

Australia: Bearing Surface Variation



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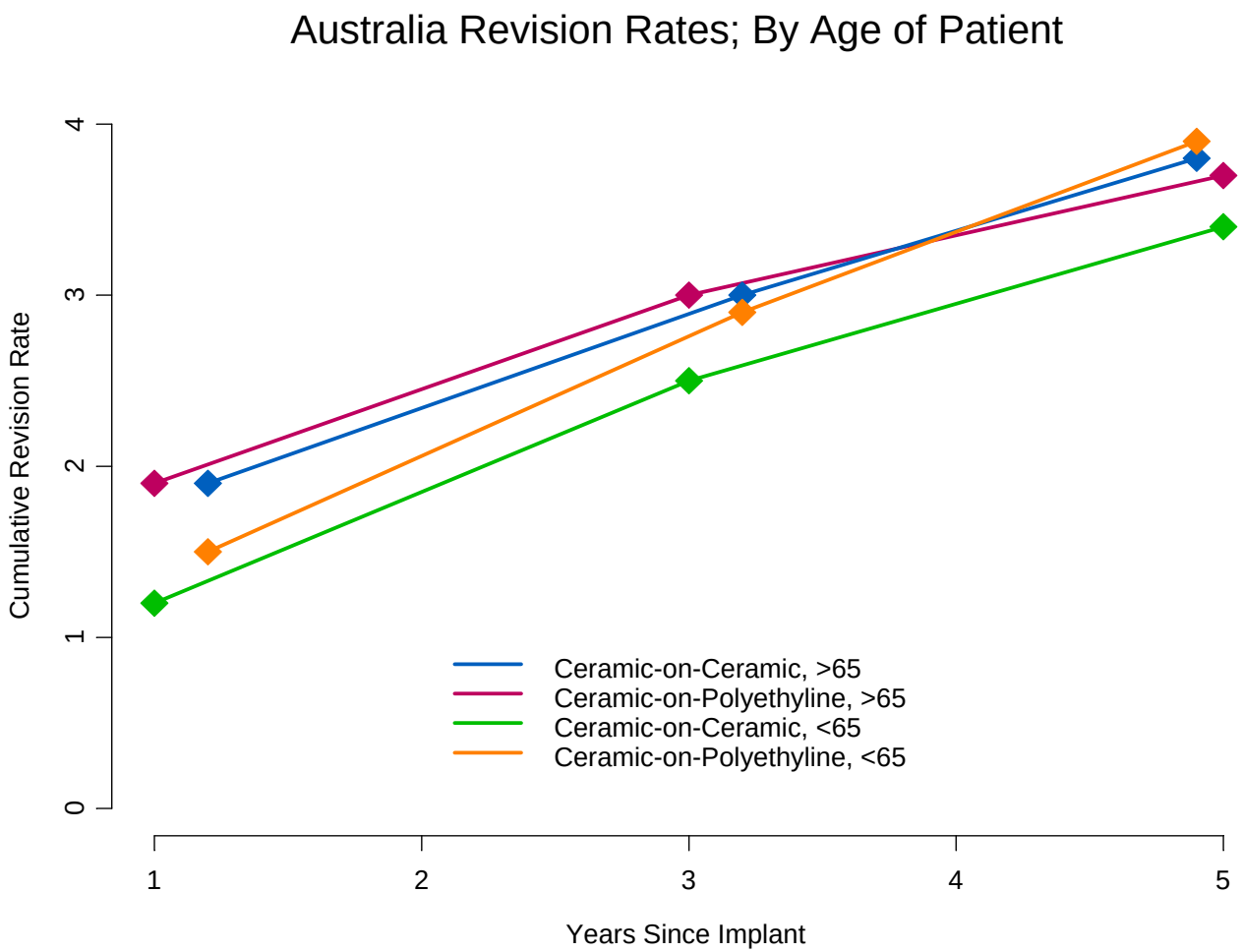
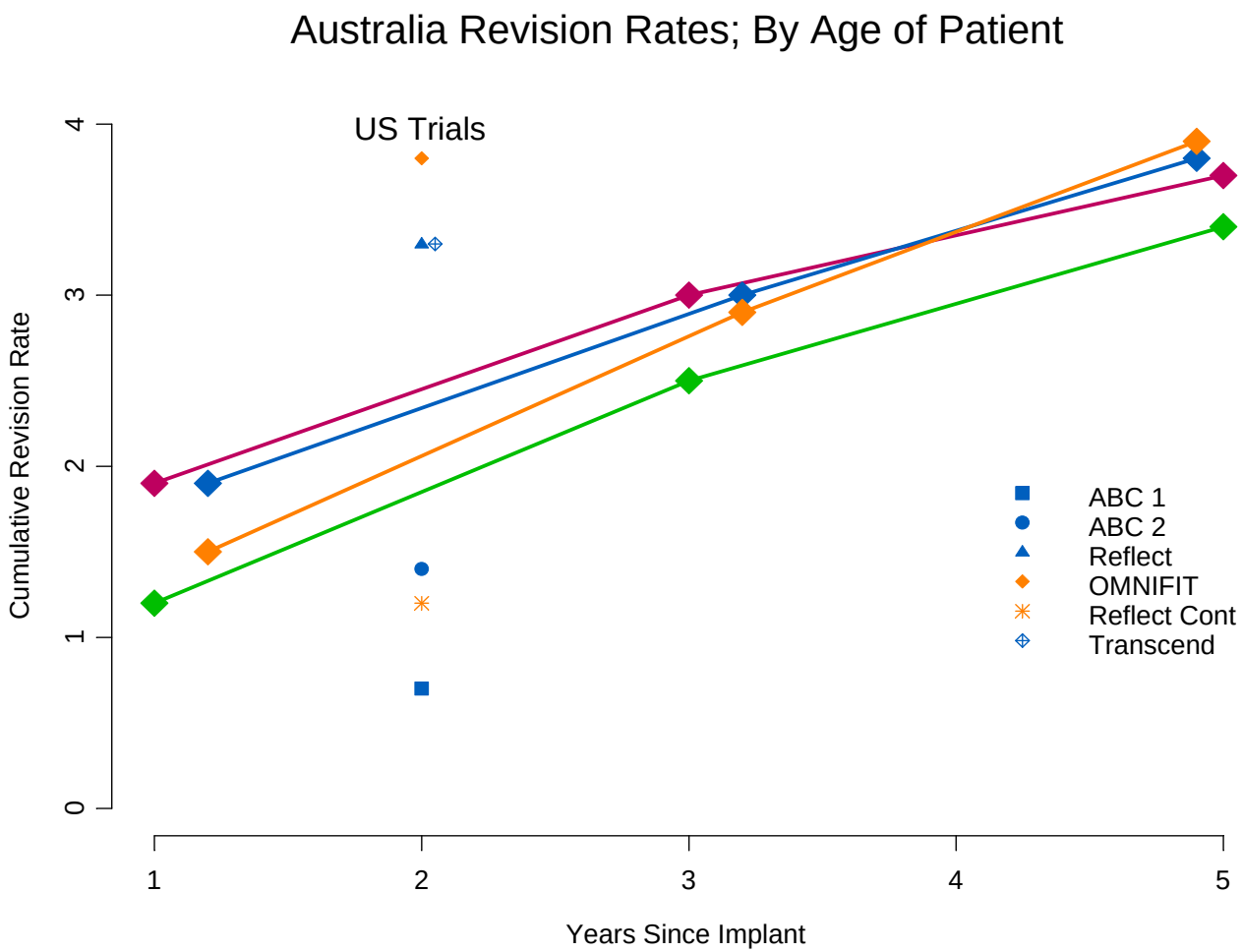


Australia & USA: Bearing Surface Variation



UK Warning Issued April 22, 2010

BRITISH ORTHOPAEDIC ASSOCIATION

BRITISH HIP SOCIETY

ADVICE TO PATIENTS WITH METAL ON METAL HIPS

The MHRA, which is the Regulatory Body responsible for hip replacement devices, has today issued an alert to all hospitals and doctors in the United Kingdom. The reason that they have done this is that there have been some reports of adverse reactions to the wear particles in metal-on-metal bearing artificial hips.

Metal-on-metal hips can either be total hip replacements or hip resurfacing procedures.

The incidence of this problem is low and is somewhere between one and nine patients in every thousand fitted with metal-on-metal bearings. As you know, the reason your surgeon fitted a metal-on-metal bearing was because the published results show metal bearings to have very low wear rates.

The problem that has been reported is that some patients have developed significant pain associated with damage to the soft tissues around the hip. A lot of research is being carried out in many Centres to see how and why this happens.
In the meantime, we can give the following advice:

- If you have no pain and you are being followed up, you need do nothing else. You will remain on regular follow-up.
- If you are not sure whether you have a metal-on-metal hip replacement or resurfacing, contact the hospital or surgeon where the operation was performed and they will be able to tell you. Most hip replacements in the United Kingdom are not metal-on-metal bearings.

If you have a metal-on-metal hip, then contact your hospital and they will arrange an outpatient assessment for you. It should be stressed that if you have a metal-on-metal hip and no pain, the chances of you being affected are extremely small.

If you do have pain, then the MHRA suggests that this should be investigated. Your surgeon will be able to do this and some tests may be helpful. These include a blood test to measure the cobalt and chromium ions in your blood and an MRI or an ultrasound scan may also be helpful.

All Orthopaedic Surgeons in the country have been informed of this and the British Orthopaedic Association and the British Hip Society will update surgeons and patients as more information becomes available.