

# Is it the time to re-invent our approach to CVOT?



QuintilesIMS™

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# Disclosure Statements and Acknowledgements



I am a full time employee of QuintilesIMS, which conducts CVOT.

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Views expressed are my mine.

# Overview

- What has changed since the 2008 FDA Guidance for Industry for new antidiabetic medications?
- Why consider updating recommended approaches to evaluating CVO?
- What key features might new approaches include?
- Discussion

# FDA Industry Guidance on CVOT in Diabetes

In 2008 FDA published recommendations

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate in a blinded fashion CV events during all phase 2 and phase 3 trials.
- Events should include CV mortality, MI infarction and stroke and “can include” hospitalization for acute coronary syndrome, urgent revascularization procedures and possibly other endpoints.
- Studies should include patients at higher risk of CV events, including elderly, etc.
- “It is likely that controlled trials will need to last more than the typical 3-6 months duration ....(“e.g., minimum 2 years” of follow-up)

FDA Guidance for Industry. Diabetes Mellitus – Evaluating cardiovascular risk in new antidiabetic therapies to treat T2DM. 2008

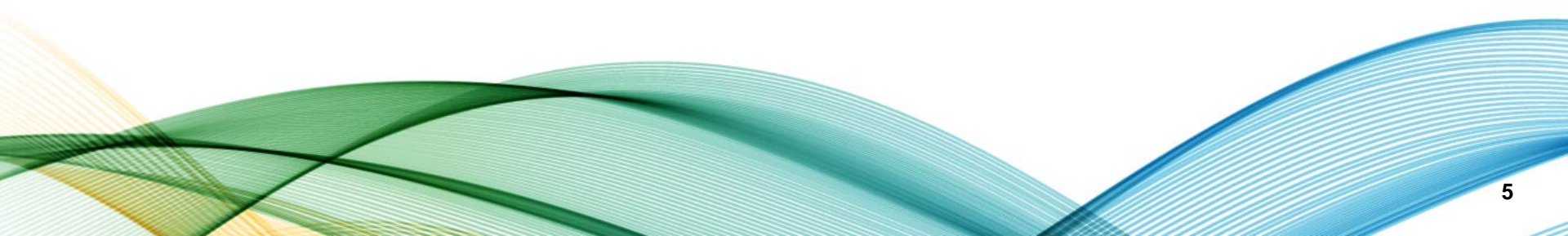
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# Some new developments since 2008



# Using patient-reported data for pharmacovigilance

## Pilot Study Conducted with European Medicines Agency

### Situation

Are data collected directly from women on medication use and other potential risk factors throughout pregnancy suitable for research purposes? Specifically

- How well can consumers report drug use and outcomes?
- How much medication usage (e.g., OTC) is not recorded in electronic health or prescription records?
- Are there additional risk factors not typically recorded?

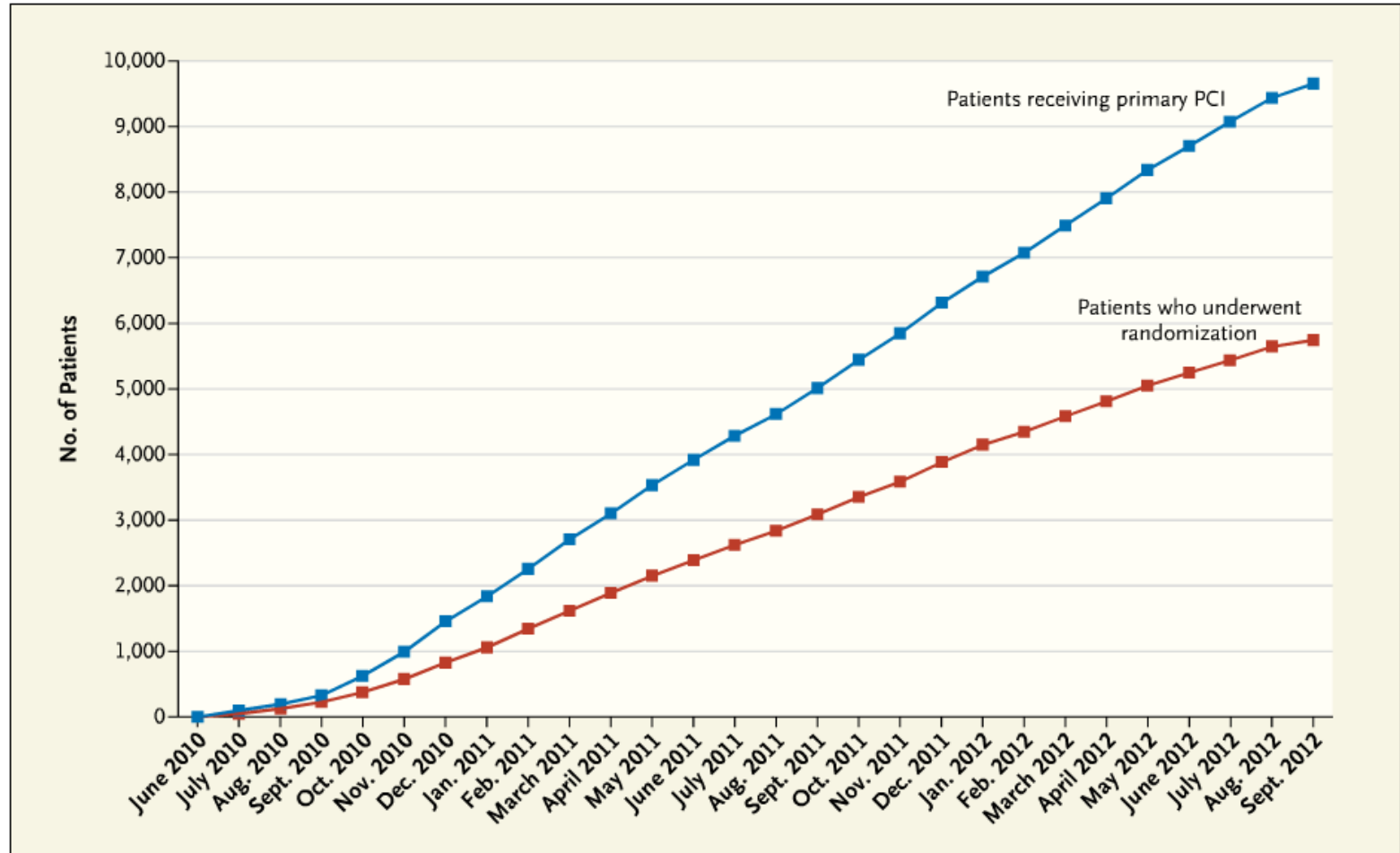
### Solution

- Compare self-reported medication use with data from electronic health records and national prescription data.
- Data collected in 4 countries, 4 languages



### Results

- 83% used  $\geq 1$  non-pregnancy-related medication during pregnancy or preceding month, 24% reported using OTC medications, 7 % reported not using prescribed medications
- Important risk factors not found in EMR were reported.
- 83% agreement with Danish National Rx register for medications for chronic use, but only 54% agreement with prescriptions written for medications indicated for short-term use.



**Rapid Randomization in the TASTE Trial, with Enrollment of Most Patients Receiving Primary Percutaneous Coronary Intervention (PCI).**

Adapted from the Institute of Medicine ([www.iom.edu/-/media/Files/Activity%20Files/Quality/VSR/LST%20Workshop/Presentations/Granger.pdf](http://www.iom.edu/-/media/Files/Activity%20Files/Quality/VSR/LST%20Workshop/Presentations/Granger.pdf)). The incremental cost of the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial was \$300,000, or \$50 for each participant who underwent randomization.



# “Randomized Registry Trial”

NEJM 2013;369:1587-97. TASTE Trial

Patients enrolled from a registry and randomized

- 7012 patients randomized from 11,709 eligible
- Also followed cohort that did not undergo randomization
- Primary end-point: all cause mortality at 30 days
- Followed entirely through existing record systems in Sweden



## Research Question

Does thrombus aspiration before PCI improve 30-day mortality?

## Answer

NO

# Pragmatic Trial in Practice



**PRESS  
RELEASE**



**STRICTLY EMBARGOED UNTIL 10.15AM FRIDAY 2 MARCH 2012**

Issued: 2 March 2012, Salford and London, UK

**Innovative UK research project to study the value  
medicines bring to patients in the real world**

**Unique collaboration to ensure medicines under development meet  
patient and healthcare system needs**

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A new way to study the value medicines bring to patients and healthcare providers has launched in the north west of England. The innovative 'real-world' research project will study the safety and effectiveness of a GlaxoSmithKline (GSK) late-stage investigational respiratory medicine alongside currently available treatments, as thousands of patients manage their chronic obstructive pulmonary

**Salford Royal**  
NHS Foundation Trust



**MANCHESTER**  
1824

The University of Manchester

# What can be gained by modifying FDA recommendations?

# Pragmatic Trials for CVO Using EMR & Claims: A Straw Man

- Randomize in diverse populations that include higher risk patients
- Compare to study drug to SoC to obtain more comparators, reflecting everyday clinical choices
- Use validation not adjudication, following tested algorithms for CVO and other outcomes of special interest
- No blinded drugs
- Require as post-marketing commitment for enhanced drug safety study, with strong encouragement to start in phase 3

# Challenges to Conducting Pragmatic CVO Trials

- Blinded drug supply is inconsistent with pragmatic approaches
  - No facilities or infrastructure to maintain, store and account for blinded drugs
- Comparing expensive new drugs to traditional drugs may be unappealing to patients or clinicians
  - May experience higher drop-out for those who were expecting to get a new drug
  - Need to equalize co-payments for patients so they are not penalized by participating in a study
- Administrative challenge to complete CRF within regular visit time window, so reliable end-point validation algorithms needed
- Deaths may be hard to find in a timely manner, since NDI has ~18 month lag

# Advantages of Pragmatic Trials for CVO

- Use same study structure to assess
  - More outcomes
  - More comparators
  - More diverse high-risk patients
  - Effectiveness as well as risk\*
- May be useful to include patient-reported data since patients can provide information about effect-modifiers that doctors may not know
- Length of follow-up can be increased at small marginal cost to evaluate delayed risks and benefits
- Less risk of fraudulent patients or outcomes

\* See Fiore LD, Lavori PW. Integrating randomized comparative effectiveness research with patient care. N Engl J Med 2016;374:2152-8.

# Pragmatic Trials: A More Flexible Approach to New Pathways?



From Adaptive Licensing to Adaptive Pathways:  
Delivering a Flexible Life-Span Approach  
to Bring New Drugs to Patients

Eichler H-G et al. Clinical Pharmacology & Therapeutics  
2015; 97(3):234-246.

# Can we do pragmatic trials with a lighter touch?



# Comparing classical and pragmatic CVOT

	PRECISION	ADAPTABLE
<b>Type of RCT</b>	Classical	Pragmatic
<b>Study drug &amp; comparators</b>	Celebrex- 100-200 mg BID vs Ibuprofen- 600-800 mg TID or Naproxen 375-500mg BID	81 vs 325 mg Aspirin QD
<b>Blinded</b>	Double Blinded	No Blinding
<b>CV End-points</b>	Clinician reported CV death, non-fatal MI & non-fatal stroke	All-cause mortality, nonfatal MI & nonfatal stroke identified thru EMR
<b>End point review</b>	Blinded clinical adjudication	Validated coding algorithms for EMR
<b>No Subjects</b>	24,000	20,000
<b>Follow-up</b>	Min 18 mos; max 42 mos	Max 30 mos
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<b>Cost per patient</b>	<b>\$15,500/pt</b>	<b>\$700/pt</b>
<b>PRICE TAG</b>	<b>\$420 M</b>	<b>\$14 M</b>

# Progress is being made on validation

**Table. Comparison of Medicare vs. Clinical Trial Outcomes at 6 months**

	Denominator	# of Events, Trial	# of Events, Medicare	Sensitivity*	Specificity*	PPV*	NPV*
Death	2766	127	129	0.99-1.00	1.00	0.96-1.00	1.00
All-cause Rehospitalization	348	177	184	0.96-0.97	0.93	0.94-0.96	0.95-0.97
MI	1598	89	89-92	0.69-0.75	0.97-0.99	0.69-0.72	0.98-0.99
Heart Failure	339	51	48-50	0.75-0.77	0.96-0.97	0.78-0.89	0.93-0.96
Any revascularization	325	43	36-43	0.74-0.91	0.98-0.99	0.89-0.91	0.96-0.99

PPV, positive predictive value; NPV, negative predictive value; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grating.

\*For each metric, a range of values is reported across 1) four individual clinical trials, 2) two methods of trial endpoint ascertainment (CEC and investigator-reported), and 3) up to four Medicare ICD 9-CM coding algorithms for each outcome.

Brennan J M et al: Comparisons of Medicare claims with clinical trial outcomes for follow-up of older individuals with acute coronary syndrome. Circulation 2014; 7:A26

## Use of Medicare Data to Identify Coronary Heart Disease Outcomes in the Women's Health Initiative

**Background**—Data collected as part of routine clinical practice could be used to detect cardiovascular outcomes in pragmatic clinical trials or clinical registry studies. The reliability of claims data for documenting outcomes is unknown.

**Methods and Results**—We linked records of Women's Health Initiative (WHI) participants aged  $\geq 65$  years to Medicare claims data and compared hospitalizations that had diagnosis codes for acute myocardial infarction or coronary revascularization with WHI outcomes adjudicated by study physicians. We then compared the hazard ratios for active versus placebo hormone therapy based solely on WHI-adjudicated events with corresponding hazard ratios based solely on claims data for the same hormone trial participants. Agreement between WHI-adjudicated outcomes and Medicare claims was good for the diagnosis of myocardial infarction ( $\kappa$ , 0.71–0.74) and excellent for coronary revascularization ( $\kappa$ , 0.88–0.91). The hormone:placebo hazard ratio for clinical myocardial infarction was 1.31 (95% confidence interval, 1.03–1.67) based on WHI outcomes and 1.29 (95% confidence interval, 1.00–1.68) based on Medicare data. The hazard ratio for coronary revascularization was 1.09 (95% confidence interval, 0.88–1.35) based on WHI outcomes and 1.10 (95% confidence interval, 0.89–1.35) based on Medicare data. The differences between hazard ratios derived from WHI and Medicare data were not significant in 1000 bootstrap replications.

**Conclusions**—Medicare claims may provide useful data on coronary heart disease outcomes among patients aged  $\geq 65$  years in clinical research studies.

**Clinical Trials Registration Information**—URL: [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Unique identifier: NCT00000611.  
(*Circ Cardiovasc Qual Outcomes*. 2014;7:157-162.)

“**THEY ALWAYS  
SAY TIME CHANGES  
THINGS, BUT YOU  
ACTUALLY HAVE TO  
CHANGE THEM  
YOURSELF.**”

**- ANDY WARHOL**

# Contact Information



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