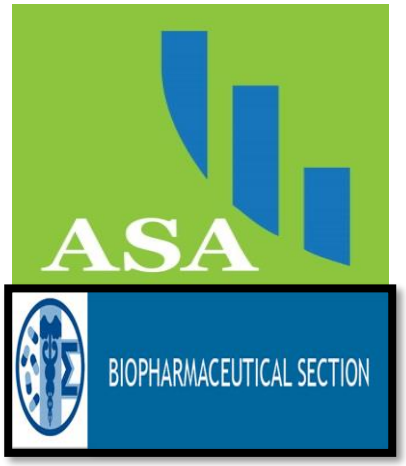

Integration of continuum safety evidence for decision making

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ASA Biopharmaceutical Section
Regulatory-Industry Statistics Workshop
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Acknowledgement and Disclaimer

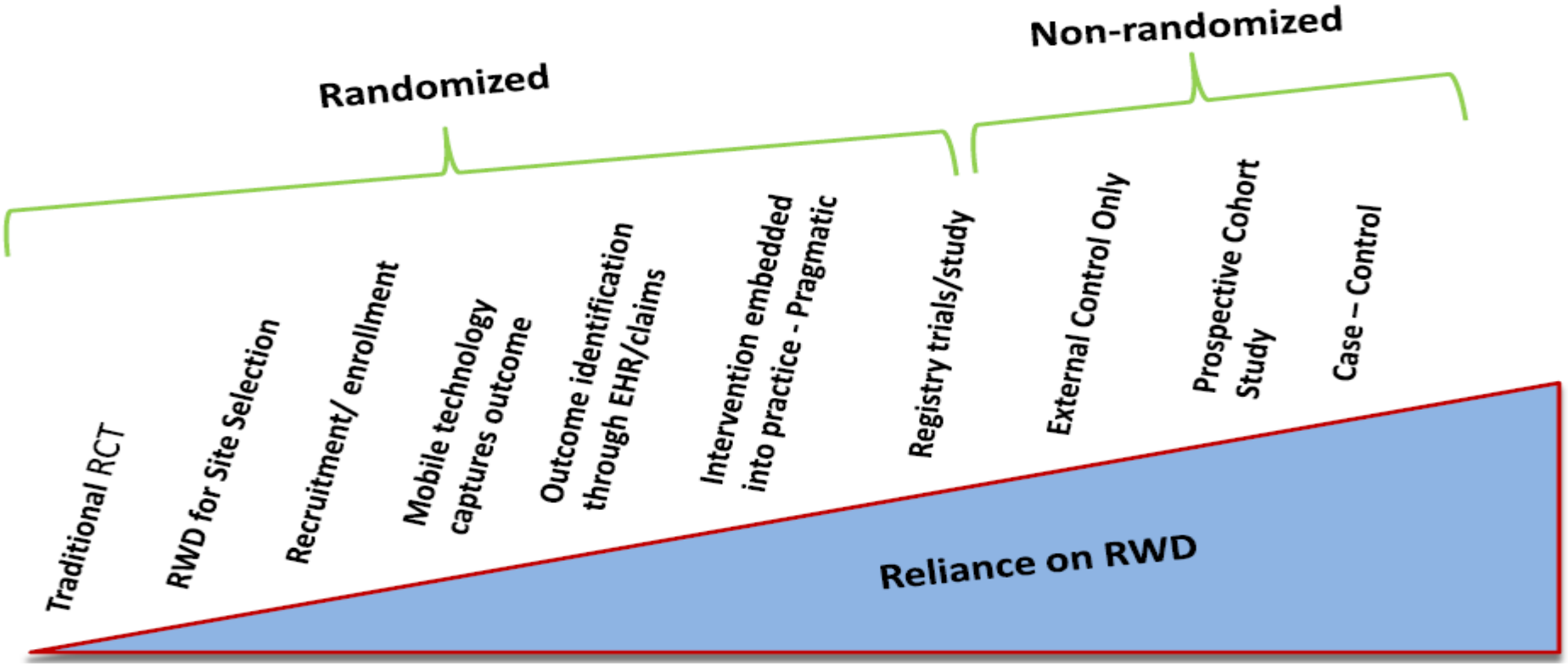
- Acknowledgement:
  - ASA BIOP Safety Working Group RCT/RWE working stream

- Disclaimer:
  - The opinions provided here are reflective of presenter's view and may not represent those of their employers

Agenda

- Motivating example
- Continuum safety evidence – reconciling with multisource data
- Study strategies for RCT and RWE evidence integration
- Concluding Remarks

Spectrum of Reliance on RWD



* Based on a presentation by Dr Aloka Chakravarty of US FDA at the UMBC-Stanford Statistics Workshop Sep 14 2018

Motivating example

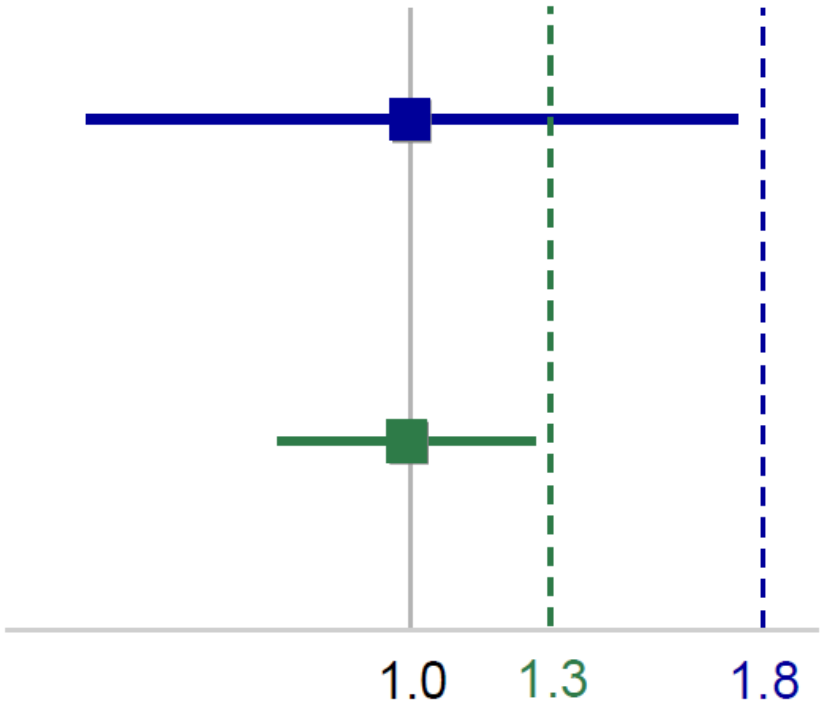
Motivating example: CVOT

- December 2008, US FDA issued guidance to require cardiovascular outcomes trials for all type 2 diabetes drug candidates.

Pre-marketing Analyses
Upper Bound 95% CI <1.8

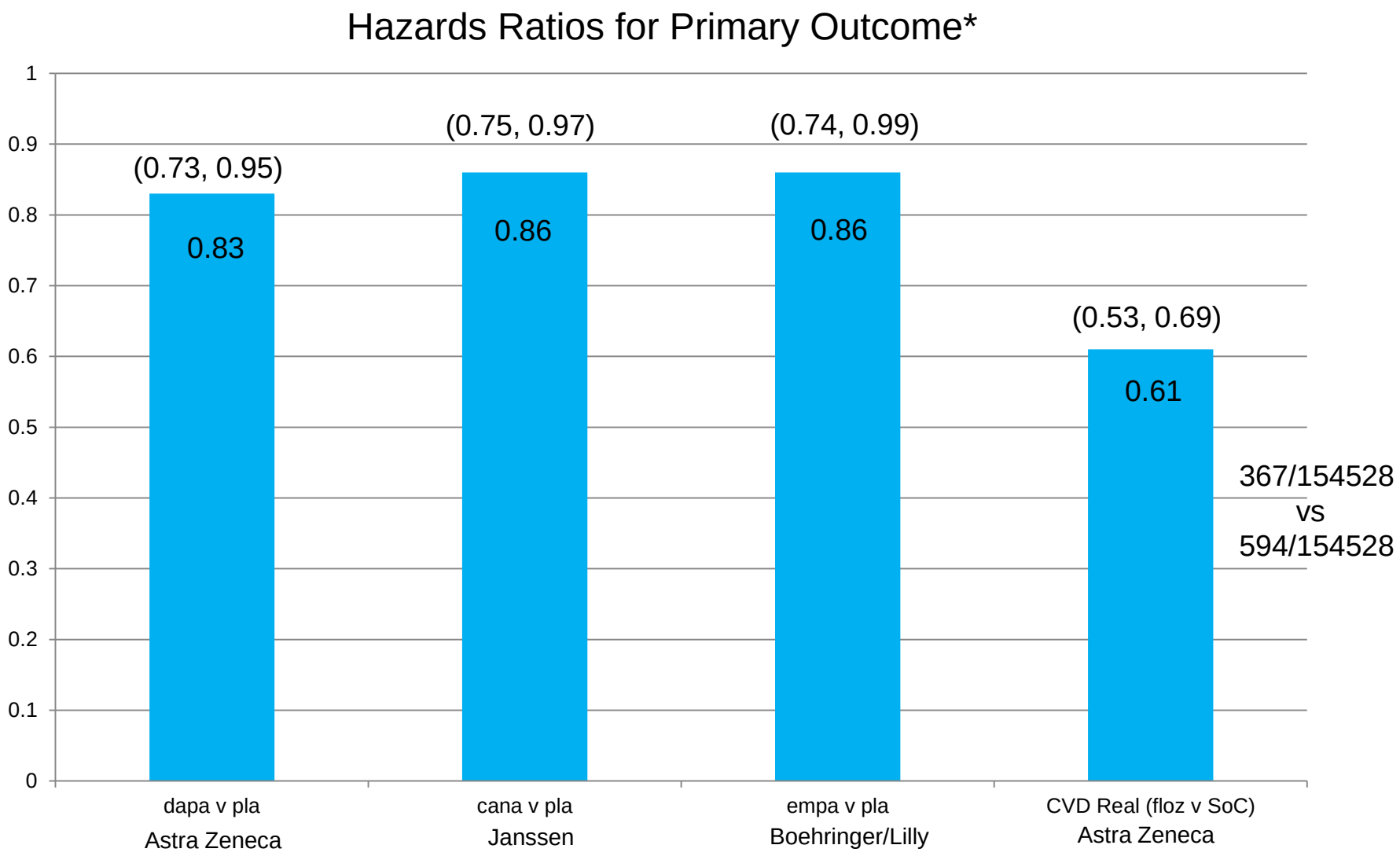
At HR=1.0; 90% power;
122 events

Post-marketing Analyses
Upper Bound 95% CI <1.3
At HR=1.0; 90% power;
611 events



* Based on a presentation by Dr Marc S. Sabatine at EMDAC Public Advisory Committee Meeting on 10/24/2018

Motivating example: RCT vs RWE



*Primary Outcome in CVD Real is HHF; RCTs use CVD Death/related events.

CVOT CVD-Real & related studies, some demographics

Study		Age	% female	% with CD*	Base HBA1c
CVD-REAL	SGLT2 (154,528)	56.9 (10.0)	44.3	13.0	N/A
SGLT-2i vs oGLD	oGLD (154,528)	57.0 (10.6)	44.5	13.1	
DECLARE	daga (8582)	63.9 (6.8)	36.9	40.5	8.3 (1.2)
Dapagliflozin vs placebo	pla (8578)	64.0 (6.8)	37.9	40.8	8.3 (1.2)
CANVAS, C..-R	cana (5795)	63.2 (8.3)	35.1	71.2	8.2 (0.9)
canagliflozin vs placebo	pla (4347)	63.4 (8.2)	36.7	73.5	8.2 (0.9)
EMPA-REG OUT.	empa (4687)	63.1 (8.6)	28.8	99.4	8.07 (0.85)
empagliflozin vs Placebo	pla (2333)	63.2 (8.8)	28.0	98.9	8.08 (0.84)

*CD (cardiovascular disease) summarized somewhat differently in each study. Attempt made to use most comparable or broadest terms.

Motivating example: CVOT in RA – (tocilizumab vs TNFi)

- ENTRACTE – a CVOT study required by FDA for tocilizumab vs etanercept (a TNF inhibitor)
- Two RWE studies showed that tocilizumab vs TNFi drugs showed no statistical differences between treatments. The first (Kim et al) completed before the ENTRACTE study results were publicly known.

ENTRACTE	HR=1.05 95%CI (0.77,1.43)	
RWE 1 (Kim et al) 9,218 TCZ and 18,810 TNFi (3 different obs DBs)	HR_{pooled}=0.84 95%CI (0.56,1.26)	
RWE 2 (Xie et al)	$HR_{Medicare}$=0.79 95% CI (0.65, 0.96) $HR_{MarketScan}$=0.84 95% CI (0.52, 1.37)	Medicare and MarketScan were 2 of the 3 DBs used in Kim et al

Kim and Schneeweiss. When Randomized Clinical Trials and Real-World Evidence Say the Same: Tocilizumab and its Cardiovascular Safety; Arthritis Rheumatol. 2019 Aug 30
Kim SC, et al. Cardiovascular Safety of Tocilizumab Versus Tumor Necrosis Factor Inhibitors in Patients With Rheumatoid Arthritis: A Multi-Database Cohort Study. Arthritis Rheumatol. 2017;69(6):1154-64
Xie F et al. Tocilizumab and the Risk of Cardiovascular Disease: Direct Comparison Among Biologic Disease-Modifying Antirheumatic Drugs for Rheumatoid Arthritis Patients. Arthritis Care Res. 2019;71(8):1004-18

Motivating example: CVOT Summary (1)

- SGLT-2i example illustrates similarities and differences between RCT CVOTs and RWE CVOT
  - Population: e.g., RWE somewhat younger
  - Measurement: Less information documented in data sources
  - Outcome: No formal adjudication but RWE uses validated algorithms
- What does this suggest about RWE for decision making?
  - CVOT RWE may require some extra data collection / validation
  - Control groups may still needed

Motivating example: CVOT Summary (2)

- Tocilizumab vs TNFi example additionally outlines how RWEs can
  - Add complementary data sources to RCTs
  - Work well when designed to closely match RCTs design parameters
  - Aid in regulatory decision making
- It also points to a need for RWE design work to
  - Do systematic comparisons of RWEs and RCTs to know where they can complement each other

Multi-source of safety data

Sources of Safe Data

- Clinical trials
- Spontaneous adverse event reporting databases
  - FAERS and VAERS
  - EudraVigilance and VAESCO
  - Vigibase
- Electronic healthcare databases
- Administrative and health claims databases
- Patient generated data
- Registries
- Pragmatic trials

Multisource data and FDA safety questions

from Rima Izem's (formerly of FDA) presentation at 2018 conference

Product and Adverse Event	**FDA Action**	**Observational Study Evidence**
New anticoagulants and bleeding	Drug safety communications; conduct multilple FDA led studies (CMS, Sentinel)	FAERS, published studies
PDE-5 inhibitors and Non-arteritic anterior ischemic optic neuropath (NAION)	Drug Safety Alert, Post-market safety studies commitment, labelling changes	FAERS, sponsor-led post-market comparative safety studies
Testosterone products and CV outcomes	Labeling changes, drug saety communications. Require sponsor-led CVOTs	Drug use, published comparative safety studies
TNF blockers and pregnancy related outccomes	Labelling changes	Completion of sponsor-led pregnancy studies and published evidence

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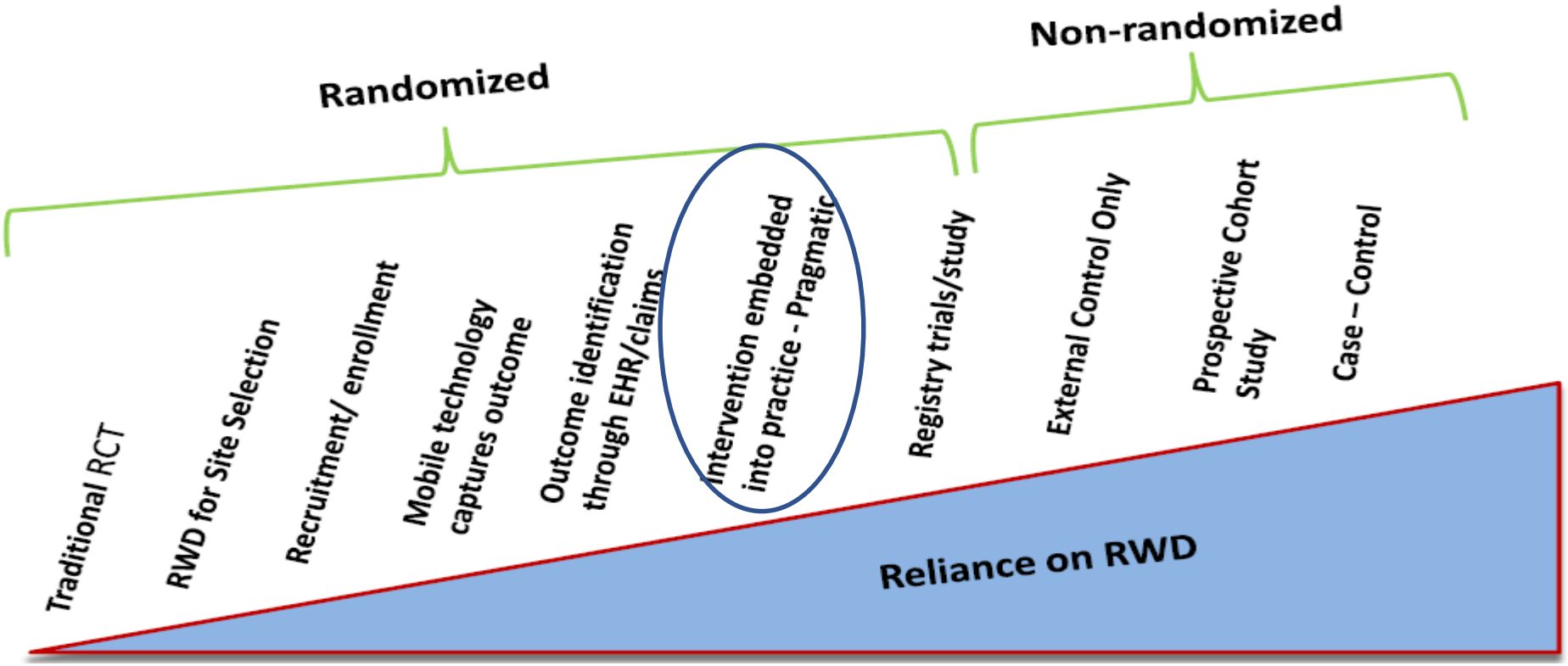
Poor Algorithms in Administrative Claims DBs

- Examples of outcomes with poor PPV
  - acute liver failure
  - acute renal failure
- Examples of exposure or covariates with misclassification or missing values
  - Smoking status over time (or specific pack-years)
  - Lab values
  - Exposure to over the counter drugs

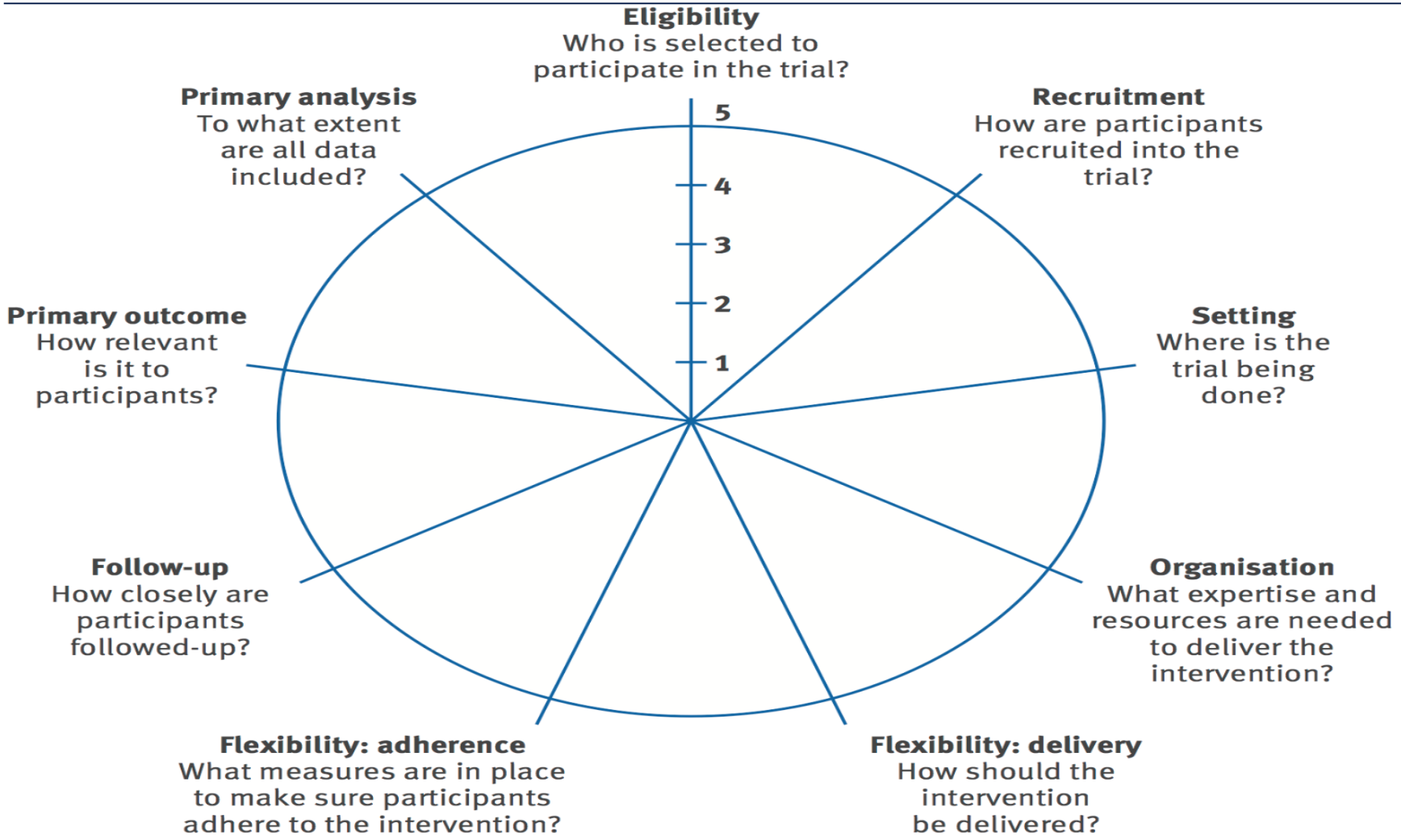
Continuum of safety evidence and pragmatic studies

Spectrum of Reliance on RWD



* Based on a presentation by Dr Aloka Chakravarty of US FDA at the UMBC-Stanford Statistics Workshop Sep 14 2018

PRECIS – PRagmatic Explanatory Continuum Indicator Summary- tool which helps to determine how pragmatic or explanatory trial is



www.precis-2.org with specific trial PRECIS score
https://w3.abdn.ac.uk/hsru/Precis/Trials

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Pragmatic trial or observational study?

- A case study: *Evenity* (romosozumab) is Amgen's investigational bone-forming monoclonal agent for the treatment of osteoporosis. It's designed to improve bone mass, structure and strength by both increasing bone formation and decreasing bone resorption.

- At a Jan 16, 2019 FDA Advisory Committee meeting, most committee members voted to recommend approval for Evenity for the treatment of osteoporosis in postmenopausal women at high risk of fracture.

Pragmatic trial or observational study?

- The meeting largely focused on Evenity's potential cardiovascular risk signal, as the drug demonstrated a higher incidence of major adverse cardiovascular events (MACE) in one of the two major clinical trials.

	Trial 337		Trial 142	
	Placebo (N=3576)	Romosozumab (N=3581)	Alendronate (N=2014)	Romosozumab (N=2040)
MACE, n (%)	29 (0.8)	30 (0.8)	22 (1.1)	41 (2.0)
CV death	15 (0.4)	17 (0.5)	12 (0.6)	17 (0.8)
Nonfatal myocardial infarction	8 (0.2)	9 (0.3)	5 (0.2)	16 (0.8)
Nonfatal stroke	10 (0.3)	8 (0.2)	7 (0.3)	13 (0.6)

* Based on a presentation by Dr Jacqueline Karp at ACRHD Advisory Committee Meeting on 1/16/2019

Pragmatic trial or observational study?

- FDA's meta-analysis of the trial data did not suggest that differences in cardiovascular risk factors between the populations of the two major trials contributed to the disparities in MACE and CV SAE data.

Analysis Model	Study	Comparison	Primary Endpoint	HR (95% CI) †
Meta-Anaylsis	337 & 142	Romosozumab vs. Comparator	MACE	1.38 (0.96 – 1.99)

Analysis Model	Study	Comparison	Primary Endpoint	HR (95% CI) †
Network Meta-Analysis	337	Romosozumab vs. Placebo (Direct)	MACE	1.03 (0.62 – 1.72)
	337 & 142	Alendronate vs. Placebo (Indirect)	MACE	0.55 (0.27 – 1.14)

†All hazard ratios are estimated based on 12-month double blind period

* Based on a presentation by Dr Tae Hyun Jung at ACRHD Advisory Committee Meeting on 1/16/2019

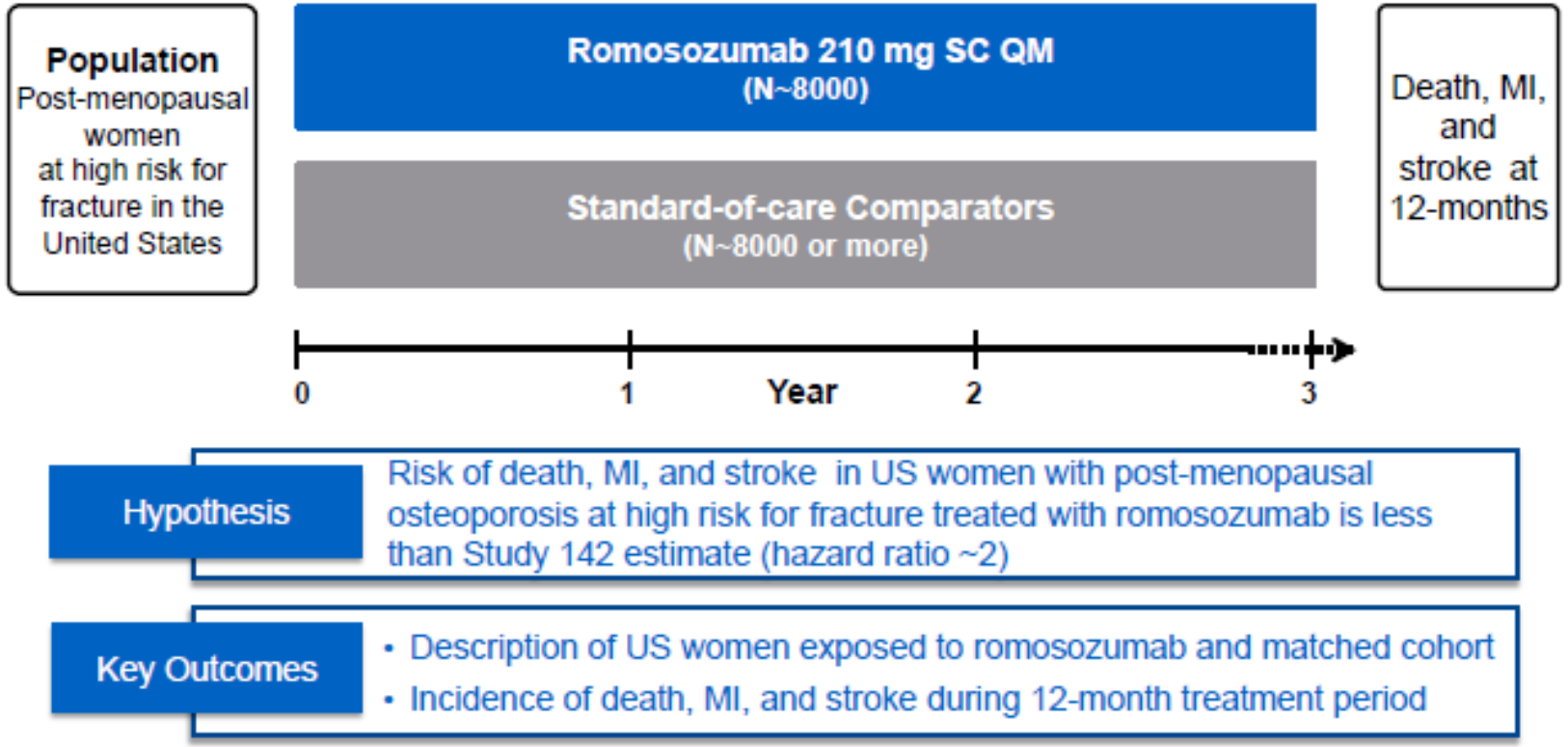
Pragmatic trial or observational study?

- There was a general agreement among the panel that the cardiovascular risk could be studied in the postmarket phase. However, the committee was split roughly 50/50 over the type of study that should be required.
- Tobias Gerhard, a professor of pharmacoepidemiology at Rutgers University, favored a pragmatic trial "I would encourage FDA and the sponsor to think about innovative, …, and try to find a way to do a pragmatic trial that has baseline randomization, which uses a lot of the methodology using existing databases ..."
- FDA presented feasibility of observational study, and raised concerns that residual confounding and selection bias may impact the interpretability of observational postmarket studies. An observational study would be insufficient and called for a "rigorous" cardiovascular outcomes study.

Pragmatic trial or observational study?

- Amgen proposed evaluating the cardiovascular risk further with a postmarketing observational study.

Proposed Real-world Observational Comparative Safety Study Design

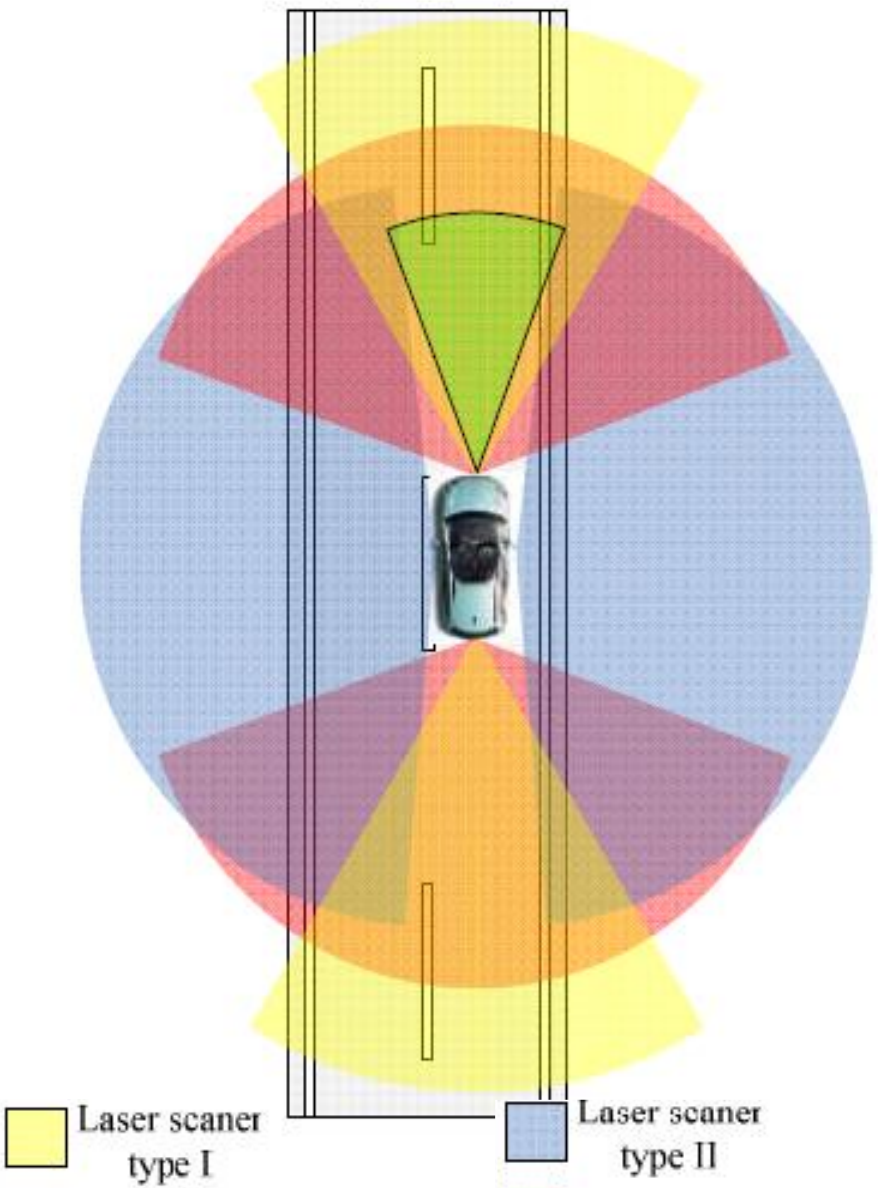


Pragmatic trial or observational study?

- April 9, 2019, US FDA approved Evenity for the treatment of osteoporosis in postmenopausal women at high risk for fracture.
  - Narrowed indication for patients at low CV risk, and a black box notes that Evenity may increase the risk of myocardial infarction, stroke and CV death.
  - FDA required Amgen to conduct "a five-year observational feasibility study, potentially followed by a comparative safety study or trial to rule out an unacceptable increase in risk of MI, stroke, and cardiovascular death among users of Evenity compared to users of an appropriate comparator(s)"

Design Methods for RCT and RWE evidence integration

Classification of Evidence Integration methods



- Complementary: when the information provided by the input sources represents different parts of the scene and could thus be used to obtain more complete global information.
- Redundant: when two or more input sources provide information about the same target and could thus be fused to increment the confidence.
- Cooperative: when the provided information is combined into new information that is typically more complex than the original information.

Radar

Camera

Complementary

- The 2018 US FDA RWE framework states, “Although observational studies may provide credible evidence, there is a stronger scientific justification for deriving evidence of a drug effect from randomized controlled trials as compared to observational studies,”

- Analyses of RWE studies are useful supplements to clinical trials for generating evidence on the effectiveness, harm, use, and value of medical products in routine care.

- Results using observational studies concordant with the pivotal clinical trial can provide regulators with greater confidence in approving the new medication, whereas discordant results could warrant deeper reexamination of the clinical trial or nonrandomized data.

Redundant

- Practical applications of meta-analysis are usually limited to synthesizing evidence from RCTs. Meta-analysis frequently disregard observational evidence from NRSs because it is commonly assumed that estimates of relative treatment effects are more likely to be biased, especially when confounding has been inadequately addressed.

- When non-randomized evidence is included in an meta-analysis, this increases concerns about intransitivity and inconsistency of the method, and that results may be very precise, yet biased. However, interest in including NRSs in the meta-analysis synthesis and decision-making process is growing.

- Although RCTs are the most reliable source of information on relative treatment effects, their strictly experimental setting and inclusion criteria may limit their ability to predict results in real-world clinical practice. NRS-based estimates of treatment effects may complement evidence provided by RCTs, and potentially address some of their limitations.

Cooperative

- Current gaps or perceived obstacles to increasing use of real-world data include insufficient confidence for validating electronic health record and claims data and also integrating these with clinical data.*

- If “real-world” sources like insurance claims or electronic health records can replicate previously known results from randomized clinical trials, real-world evidence can be used to complement or supplement current randomized controlled clinical trial data.

* Lamberti, Mary Jo, et al. "The Use of Real-World Evidence and Data in Clinical Research and Postapproval Safety Studies." *Therapeutic innovation & regulatory science* 52.6 (2018): 778-783.

Cooperative

- The combination of traditional development pathways and an array of accelerated pathways provide the FDA with considerable flexibility to encourage manufacturers to match the level of evidence with the clinical indication (**while still maintaining the RCT as the cornerstone**). Such flexible use of real-world evidence could lead to the incorporation of many more indications into labeling and boost efforts to optimize the evidence base for health and health care.*

- To replicate the known RCT results, parameters such as inclusion/exclusion criteria and exposure and outcome definitions will be designed to match the clinical trial as much as possible.

- If reproducibility is achieved, a causal biologic relationship is more likely.

* Califf, R. M. (2018). Comparison of Observational Data and the ONTARGET Results for Telmisartan Treatment of Hypertension: Bull's-eye or Painting the Target Around the Arrow?. *JAMA internal medicine*, *178*(1), 63-65.

Cooperative

- We propose two-phase approach:
  - Validation phase: use RWE to validate results from RCTs
  - Expansion phase: use RWE for augmenting the information from RCTs

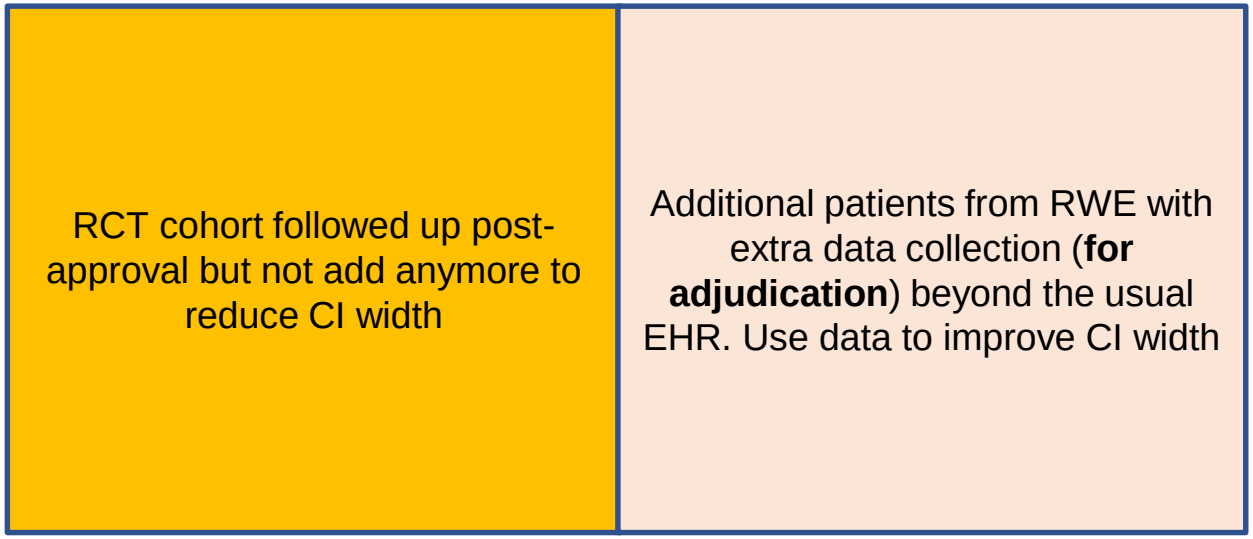
- Validation phase
  - Regular validation tools (such as ROBINS-I) + replicate the know RCT results
  - There have been previous attempts to replicate safety findings from RCTs with follow-up Sentinel queries.
  - The FDA has recently funded an initiative to replicate at least 30 published RCTs in health care claims data. The results will demonstrate whether RWE could be used to supplement or, in certain circumstances, even replace clinical trials for drug development and regulatory approval.

Cooperative

- Expansion phase
  - Effectiveness and safety in real clinical practice.
  - Long-term effectiveness and safety.
  - Support supplemental applications for effectiveness for already approved medications.
  - Revisions and refinements in existing labeling.
  - Effectiveness and safety of treatments in excluded populations from RCT.
  - Support submission for HTA/reimbursement.
  - Extend the use of the data for other potential applications.

What if SGLT 2i done in two altered steps?

- RCT to get the 1.8 upper bound prior to approval
- Convert to hybrid study to get to the 1.3 upper bound
  - Continued follow-up of all willing randomized patients
  - Add in observational data in the pragmatic (ie collect CVOT input for adjudication and HbA1c etc that not part of usual care)



Concluding Remarks

- Safety evaluation is a continuum of safety evidence from RCT to RWE.
- Proactive planning is key, not only for RCT, but also for RWE.
- The well designed and collected multi-source safety data, as well as the new analysis methodologies, can enhance our understanding on correlation, causality and prediction for safety decision making.
- Cooperative approach could be important future direction to synthesis RWE and RCT evidence. In CVOT example:
  - The RWE could replace the post marketing CVOT trial if it can replicate the results from pre-marketing RCTs.
  - The RWE (observational) could provide information to design the CVOT PCT, more generalized RCT.

Discussion

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