Advancing CAGT Trials: The Emerging Value of External Comparators

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Disclaimer

I am a full-time employee of IQVIA and perform no research or consultancy outside of that employment.

I have an adjunct assistant professor appointment at UNC-CH Dept of Epidemiology.

I accept no personal consulting fees.

None of my research activities are described here.

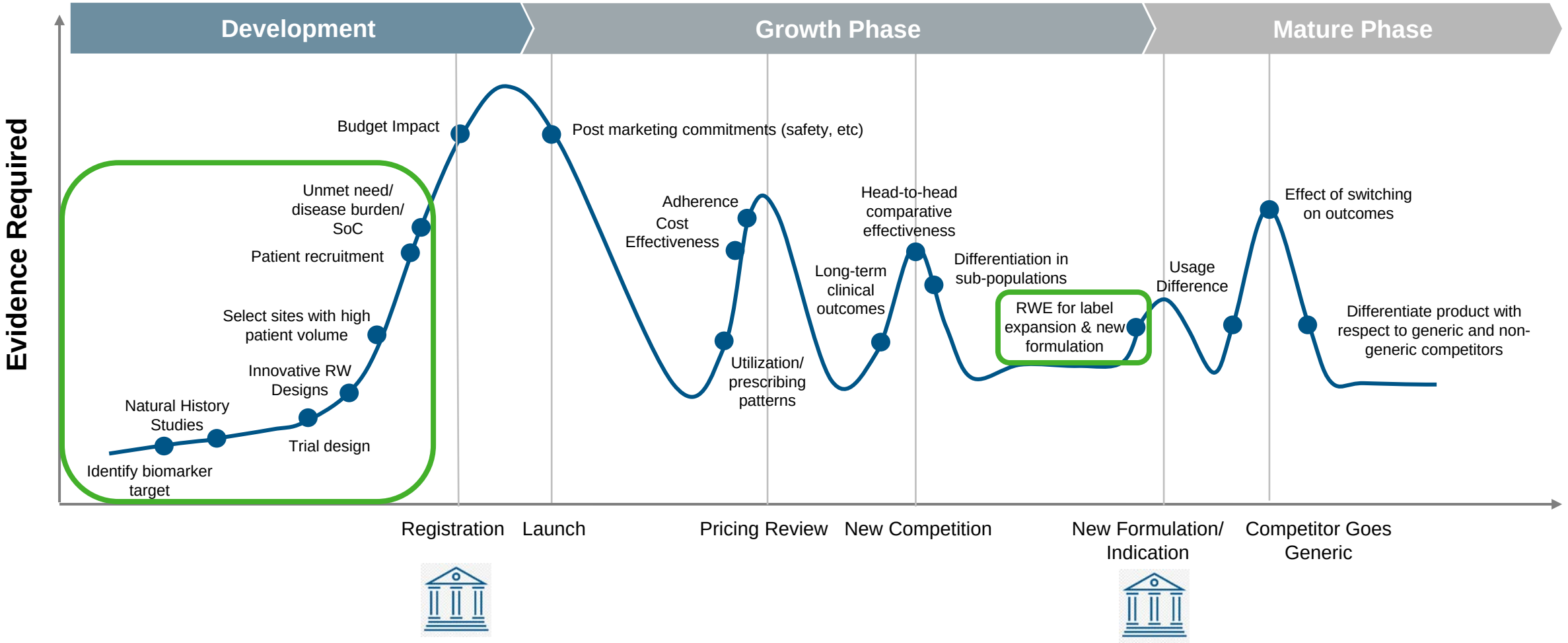
No confidential or proprietary data are included in these slides.

Presentation Overview

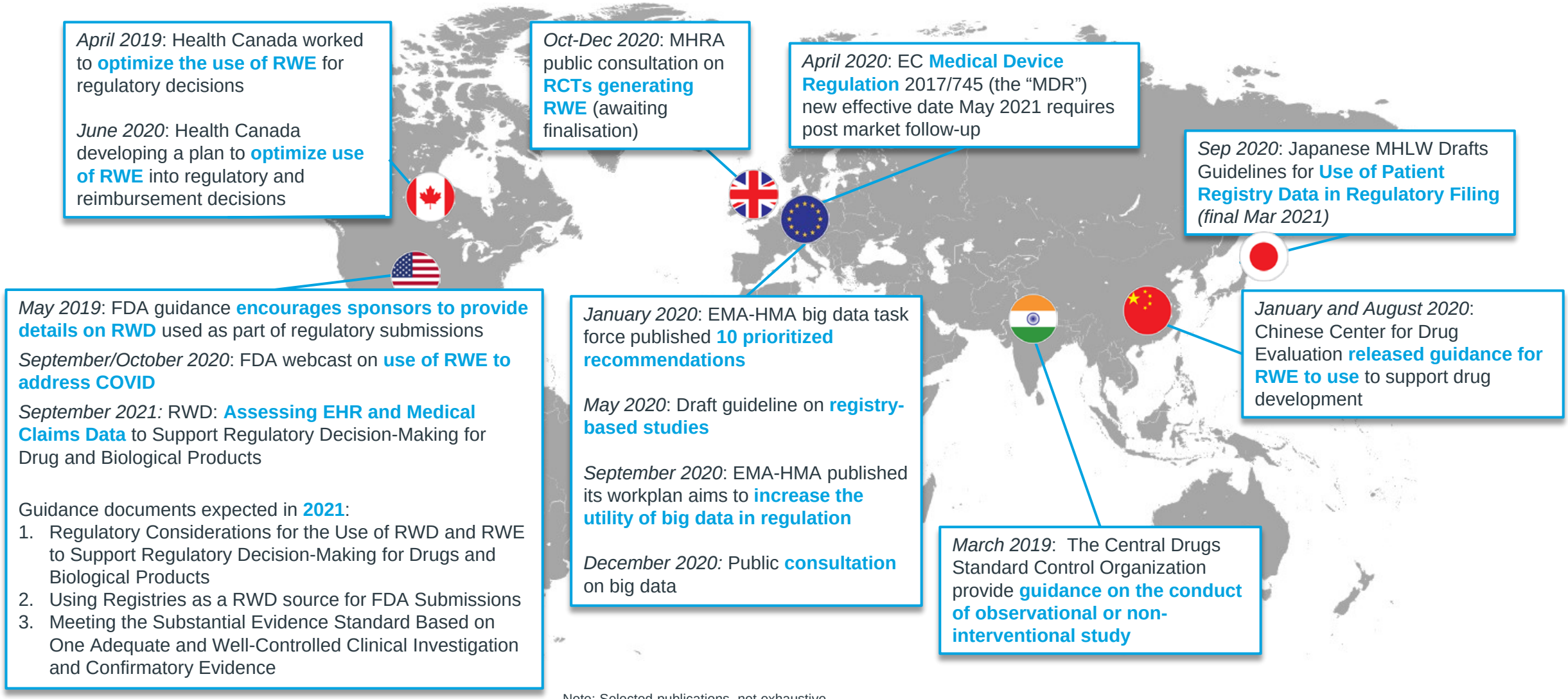
+ Introduction to RWE for CAGT drug development
+ Overview of External Comparators/Synthetic Controls
+ Use of External Controls and Lessons Learned

Real World Evidence for CAGT drug development

RWE can inform stakeholder decisions throughout the lifecycle of a product and is increasingly relevant for regulatory purposes



Regulators across the globe are beginning to recognise the potential value of RWE



April 2019: Health Canada worked to **optimize the use of RWE** for regulatory decisions

June 2020: Health Canada developing a plan to **optimize use of RWE** into regulatory and reimbursement decisions

Oct-Dec 2020: MHRA public consultation on **RCTs generating RWE** (awaiting finalisation)

April 2020: EC **Medical Device Regulation** 2017/745 (the "MDR") new effective date May 2021 requires post market follow-up

Sep 2020: Japanese MHLW Drafts Guidelines for **Use of Patient Registry Data in Regulatory Filing** *(final Mar 2021)*

May 2019: FDA guidance **encourages sponsors to provide details on RWD** used as part of regulatory submissions

September/October 2020: FDA webcast on **use of RWE to address COVID**

September 2021: RWD: **Assessing EHR and Medical Claims Data** to Support Regulatory Decision-Making for Drug and Biological Products

Guidance documents expected in **2021**:

1. Regulatory Considerations for the Use of RWD and RWE to Support Regulatory Decision-Making for Drugs and Biological Products
2. Using Registries as a RWD source for FDA Submissions
3. Meeting the Substantial Evidence Standard Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence

January 2020: EMA-HMA big data task force published **10 prioritized recommendations**

May 2020: Draft guideline on **registry-based studies**

September 2020: EMA-HMA published its workplan aims to **increase the utility of big data in regulation**

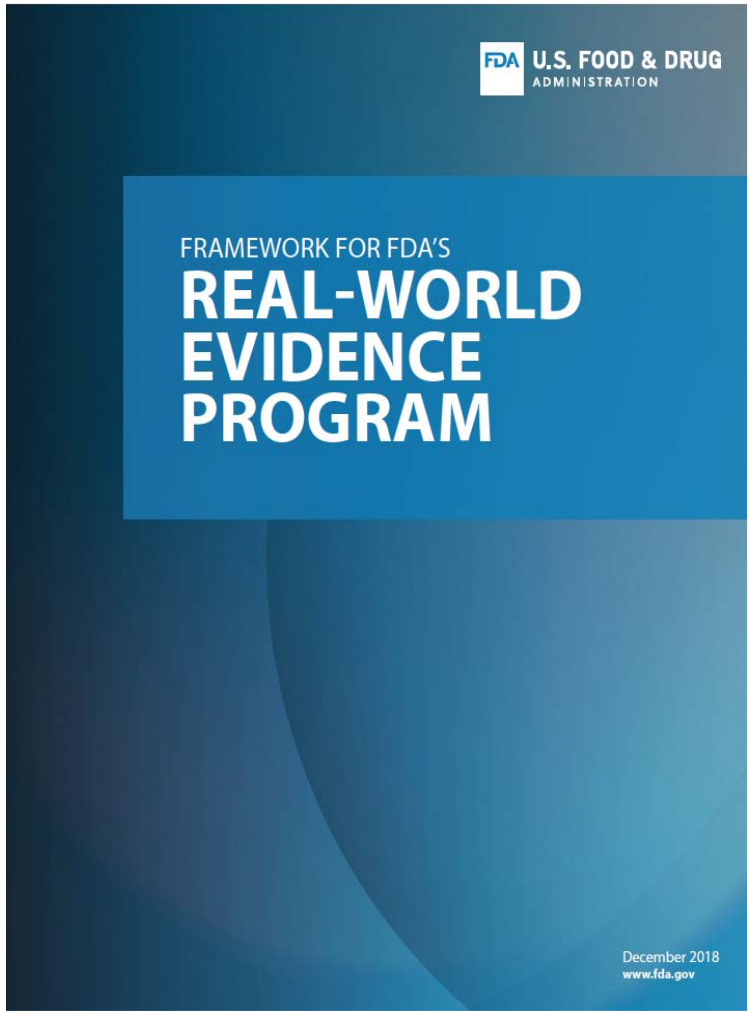
December 2020: Public **consultation** on big data

January and August 2020: Chinese Center for Drug Evaluation **released guidance for RWE to use** to support drug development

March 2019: The Central Drugs Standard Control Organization provide **guidance on the conduct of observational or non-interventional study**

Note: Selected publications, not exhaustive
PMDA - Pharmaceuticals and Medical Devices Agency; FDA – Food & Drug Administration; MoH – Ministry of Health; HMA - Heads of Medicines Agencies; EMA - European Medicines Agency

External comparators for regulatory decision-making: FDA

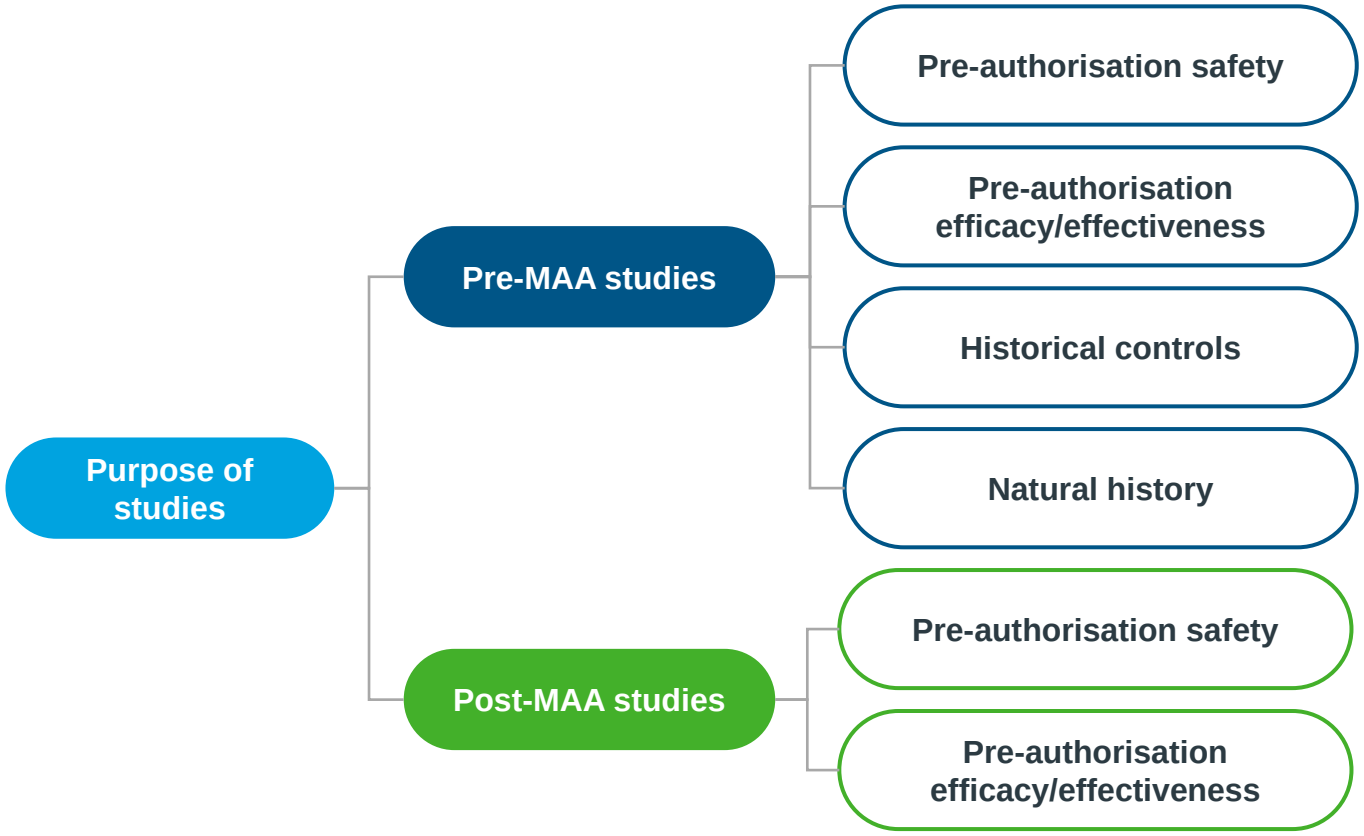


"FDA has accepted RWE to support drug product approvals, **primarily in the setting of oncology** and rare diseases. When approval is based on a **single-arm interventional trial** – often when using a parallel assignment control arm is unethical or not feasible, and **usually when the effect size is expected to be large**, based on preliminary data – the supportive RWE has consisted of data on historical response rates drawn from chart reviews, expanded access, and other practice settings"

EMA considering RWE in regulatory decision-making

Role of RWE for regulators – Primarily to address important questions that we cannot answer in standard RCTs or **to better understand single arm data when RCTs are not/less feasible**

Potential for RWE contribution?



Source: EMA "Regulatory Perspective on Real World Evidence (RWE) in scientific advice "Human Scientific Committees' Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) , Presented by Jane Moseley on 17 April 2018

An Overview of External Comparators (Synthetic Controls)

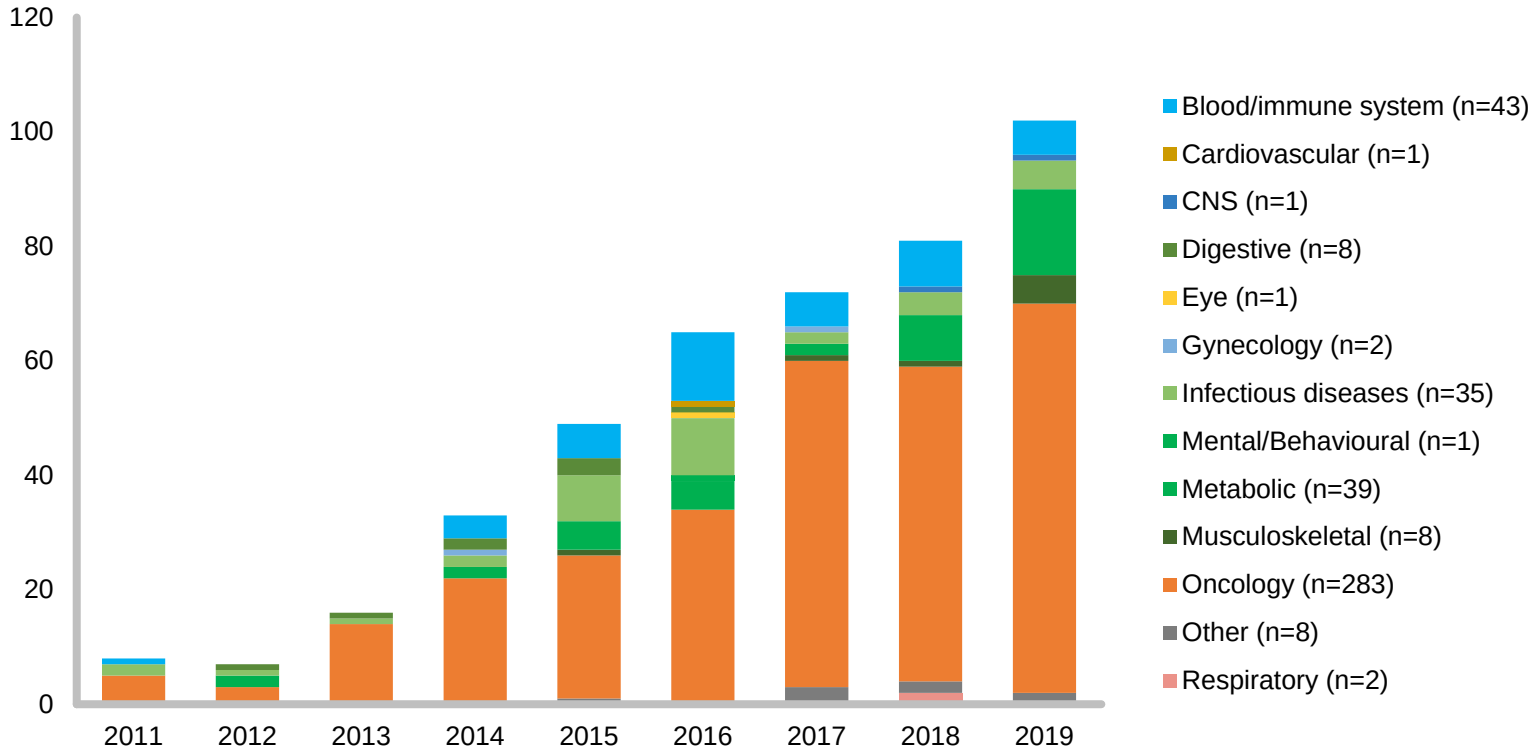
Use of single-arm trial designs is increasing and pertinent to CAGT drug development

Accelerated Approval Pathways

Advances in Precision Medicine

Growth in Rare and Orphan Pipelines

Single-arm trial submissions to HTA bodies (Jan 2011 to Dec 2019)



Source: IQVIA HTA Accelerator Analysis, March 2020

Lack of internal comparator results in challenges interpreting the data

Treatment Group

Single Arm Assignment

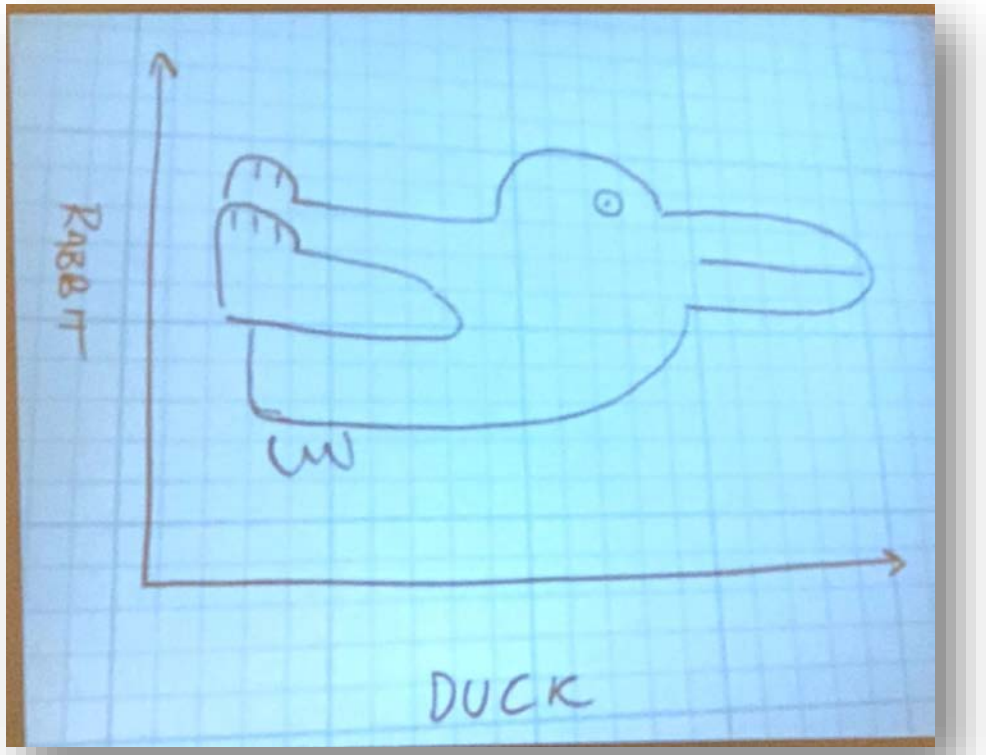


Image Source: Same Data, Multiple Perspectives: Curse of Expertise in Visual Data Communication, Cindy Xiong

An external comparator can establish context for single-arm trials

Internal Control

Not feasible because:

- Unethical to randomize
- Rare outcomes so impractical to randomize
- Patients unwilling to participate due to risk of not receiving drug

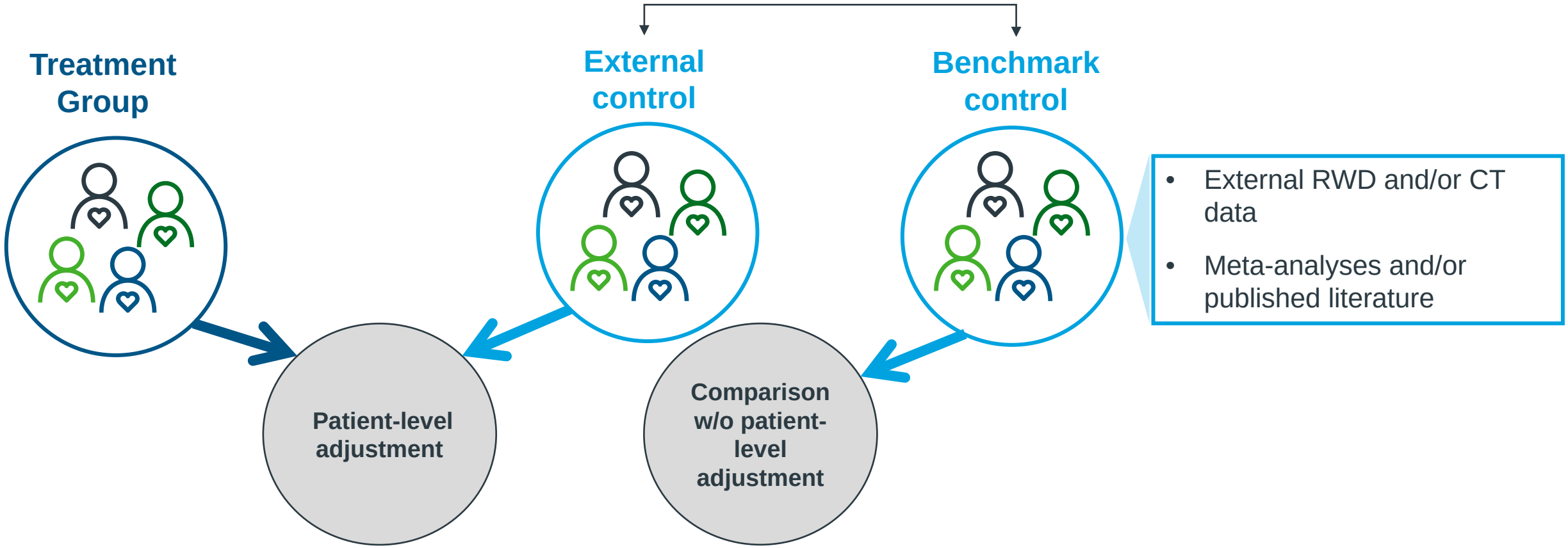
Treatment Group

External Comparator

- Patient cohort derived from real-world data (RWD)
- Patients match the inclusion / exclusion criteria for the trial
- Benchmark the efficacy data from the treatment group in a cohort of similar patients

External comparators: Terminology

External control (comparator arm, “synthetic arm”): An umbrella term referring to any control group derived from outside of the index study used as a reference to interpret efficacy outcomes from an experimental study.



Use of External Comparators

Use of External Comparators

Increased use of single-arm trials (SATs) in regulatory decision making in recent years has driven the need to contextualize outcomes

Real-world, external comparators (ECs, also known as external or synthetic controls) obtained from data on typical care have been utilized to provide this context

Randomization to standard of care or placebo in some situations may be either impractical and/or unethical

Increasing use of this approach

No guidance established to date by regulators

A growing number of regulatory decisions are informed by RWE

EC regulatory use cases, 2017-2019

			FDA		EMA	
			Approval	Label Expansion	Conditional Approval	Approval
	Product	**Indication**				
Accepted by RAs	avelumab	Metastatic Merkel cell carcinoma	(2017)		(2017)	
	cerliponase alfa	Infantile batten disease	(2017)			(2017)
	axicabtagene ciloleucel	Diffuse large B-cell lymphoma				(2018)
	tisagenlecluecel	Diffuse large B-cell lymphoma				(2018)
	omegaven	Parenteral nutrition-associated cholestasis	(2018)			
	blinatumomab	B-cell precursor acute lymphoblastic leukemia in 1st / 2nd complete remission with MRD ≥ 0.1%		(2018)		(2019)
	onasemnogene abeparvovec-xioi	Spinal muscular atrophy	(2019)			
Not accepted by RAs	selinexor	Relapsed refractory multiple myeloma	(2019)			
	tazemetostat	Epithelioid sarcoma	(2019)			
	entrectinib	ROS1-positive metastatic non-small cell lung cancer	(2019)			
	erdafitinib	Adult patients with locally advanced or metastatic urothelial cancer with FGFR2/3 mutations	(2019)			

RA= Regulatory Agency
MRD = minimal residual disease

Zolgensma for pediatric spinal muscular atrophy

Zolgensma (onasemnogene abeparvovec) was approved by the FDA on May 24, 2019 for the treatment of pediatric patients ≤2yo with spinal muscular atrophy (SMA)

Design: open-label, single-arm clinical trial and an open-label, single-arm, ascending-dose clinical trial with comparisons made to a **natural history of disease cohort of 34 SMA-1 patients**

Efficacy endpoints:

- Proportion of patients achieving the milestone of **sitting without support for at least 30 seconds** at 18 months of age
- **Survival at 14 months of age**

Natural History Study: prospective study designed to describe the current natural history of SMA-I and guide planning of clinical trials for SMA-I

Results: 1 out of 21 Zolgensma patients died before the data cut off; n=1 withdrew at 11.9 months

13 of the 19 (68%) patients continuing in the trial reached 14 months of age without permanent ventilation

Other co-primary efficacy endpoint found that **10 of the 21 patients (47.6%)** achieved the ability to sit without support for ≥ 30 seconds between 9.2 and 16.9 months of age (mean age was 12.1 months)

Based on the Nat Hx Study[1], **only approximately 25% of these patients would be expected to survive** beyond 14 months of age

[1]Finkel et al, *Neurology* 2014;83:810–817
https://www.fda.gov/media/127961/download

Tailored methods are key to success with external comparators

Key Challenges

- Selection of patients between cohorts differs, including temporality
- External comparators often use different data sources from patients in a clinical trial
- Variables between sources may have different meanings, quality, completeness

Check for updates

Commentary

DIA

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When Context Is Hard to Come By: External Comparators and How to Use Them

Christina Mack, PhD, MPH[1], Jennifer Christian, PharmD, MPH, PhD, FISPE[1], Emma Brinkley, MSc[1], Edward J. Warren, BPH[1], Marni Hall, PhD, MPH, MA[2], and Nancy Dreyer, PhD, MPH, FISPE, FDIA[3]

Drug Safety (2020) 43:623–633
https://doi.org/10.1007/s40264-020-00944-1

LEADING ARTICLE

A Framework for Methodological Choice and Evidence Assessment for Studies Using External Comparators from Real-World Data

Christen M. Gray[1] · Fiona Grimson[1] · Deborah Layton[1,2,3] · Stuart Pocock[4] · Joseph Kim[1,4,5]

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Mack C, Christian J, Brinkley E, Warren E, Hall N, Dreyer N, When Context is Hard to Come By: External Comparators and How to Use Them. TIRS. 2019
Gray CM, Grimson F, Layton D, Pocock S, Kim J. A framework for methodological choice and evidence assessment for studies using external comparators from real-world data. Drug Safety. 2020.

Regulatory assessment: lessons learned with external comparators

Results of the endpoint analyses were **largely consistent across analysis sets and sensitivity analyses.**

(FDA ODAC Briefing document)

The provided **sensitivity analysis**…and comparisons of response by ECOG category…showed –as expected…

(EMA Assessment Report)

…major challenge was to determine whether the…**rating scales were comparable** since these two studies had **different assessment times** and were conducted by **different methodologies**

(FDA Statistical Review)

Standardized analyses of response and survival were undertaken **to address these potential imbalances**…

(EMA Assessment Report)

…the use of **propensity score adjustments was successful in creating a more balanced population of …treated and control subjects** with respect to important measured baseline covariates.

(FDA ODAC Briefing document)

ECOG: Eastern Cooperative Oncology Group

Regulatory assessment: lessons learned from submissions *not* accepted

The following differences further call into question the validity of the reported historical study for this purpose…**Difference in years during which patients received treatment**..

(FDA ODAC Briefing Document)

…several methodological issues including **differential selection of…cohorts, missingness of important confounding factors, potential differential misclassification of exposures and outcomes**…

(FDA CDER Other Review)

Among the methodological issues were **confounding bias** …, **missingness** of real-world data points, **selection bias** and **temporal bias** in real-world cohort building (e.g., non-contemporaneous external cohort generation)…

(FDA CDER Other Review)

FDA considers rwORR not comparable to ORR as assessed on a clinical trial due to **differences in imaging frequency, consistency of disease burden assessment, and differences in how the endpoint is measured.**

(FDA ODAC Briefing Document)

...did not consider the RWD evidentiary due to methodological limitations, such as **post-hoc analysis**…, **selection bias**…, **confounding bias** …, and **lack of statistical power** due to limited cohort size

(FDA CDER Other Review)

rwORR: real-world objective response rate; ORR: objective response rate

Summary of the utility of external comparators for CAGT

1. With innovation comes uncertainty, but there is **clear value to having context through which to understand a CAGT product**

2. **Justify the rationale:** "…when using a parallel assignment control arm is unethical or not feasible, and usually when the effect size is expected to be large based on preliminary data"*

3. **Integrated evidence planning is important: Consider the full lifecycle** including reimbursement, from the very beginning.
   - Early engagement with regulators and payers prior to execution strengthens study and allows scientific discussion

4. **Tailor external comparators to the research question and stakeholder**
   - Regulators: most interested in similarity to the trial population
   - Payers: most interested in similarity to their population
   - Tailored methods are critical to ensure robust analysis

*Framework for FDA's Real World Evidence Program, December 2018

Thank You

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