Better Health, Brighter Future

Leveraging CADTH's Scientific Advice Program for Early Feedback: From Phase 2 Studies to RWE

CAPT Panel
October 22, 2018

Today's Participants

Panelist

Suzanne McGurn
Assistant Deputy Minister and Executive Officer, OPDP

Panelist

Amy Sood
Manager, Scientific Advice Program, CADTH

Panelist

Dr. Megan Bettle
Director, Regulatory Review of Drugs and Devices, Health Canada

Panelist

Dr. Muhammad Mamdani
Director, LKS-CHART, Professor, U of T

Panelist/Moderator

Ross Selby

Head, Global Pricing, Patient Access, and Health Economics, Takeda

What we'll discuss

- International context
- Background on CADTH's Scientific Advice Program
- Panelists' perspectives
- Discussion and Q&A

Better Health, Brighter Future

Early Scientific Advice – International Perspectives

Ross Selby, Head, Global Pricing, Market Access and Health Economics, Takeda

Heath Technology Appraisal – “Its Tough Out There!”

TLV
TANDVÅRDS- OCH LÄKEMEDELSFÖRMÅNSVERKET

HAS
HAUTE AUTORITÉ DE SANTÉ

Gemeinsamer Bundesausschuss

NICE National Institute for Health and Care Excellence

Takeda Market Access Training Camp

Early engagement can inform key development questions

What is the consequence of choosing a comparator which is not the SOC

Which countries require local data?

What effect size do we need for a premium price?

Are there critical subpopulations to consider

Which endpoints drive decision making?

What patient reported outcomes should we collect?

Is real world evidence accepted by payers?

Can we monitor long term outcomes in open label follow up?

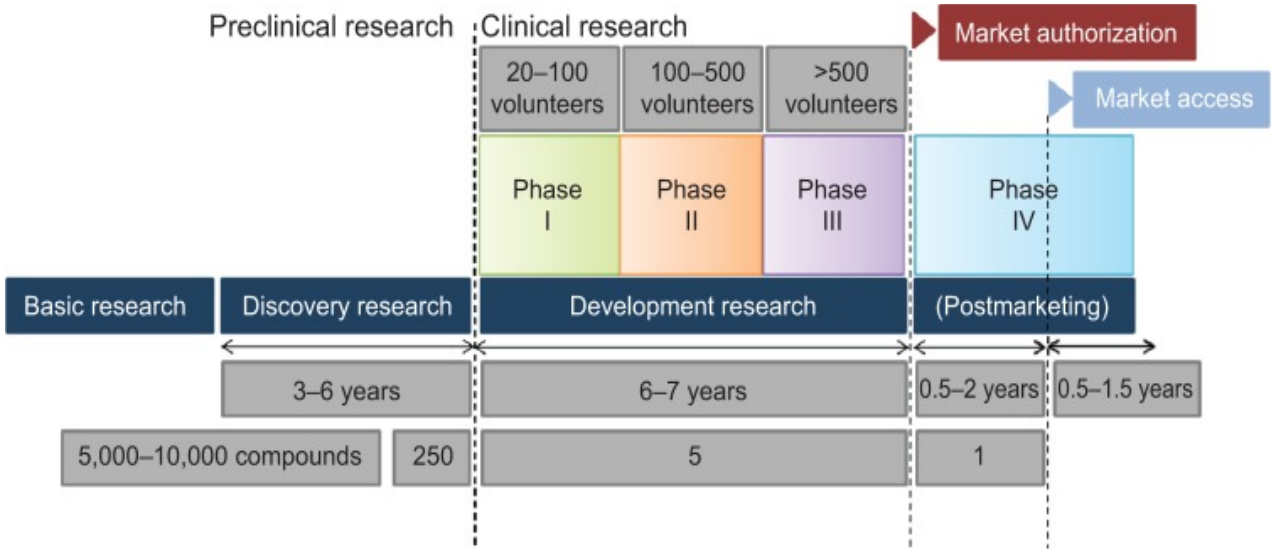
How do we distinguish what payers want vs what drives decision making?

How do we make the right trade-offs between different markets?

Why do we need early scientific advice?

- It is important to conduct early advice with HTAs for several reasons:
  - Understand the perspective of decision makers
  - Ensure that HTA insights are considered when designing studies
  - Receive insights on key issues such as population, endpoints and comparators
  - Engage early with HTAs to increase understanding, particularly in rare diseases
  - Understand additional studies or initiatives that may be required for access
  - Provide time to understand and respond to HTA concerns
  - Explore alternative strategies to address data gaps

Early advice from HTAs is needed to ensure external insights are included into evidence development



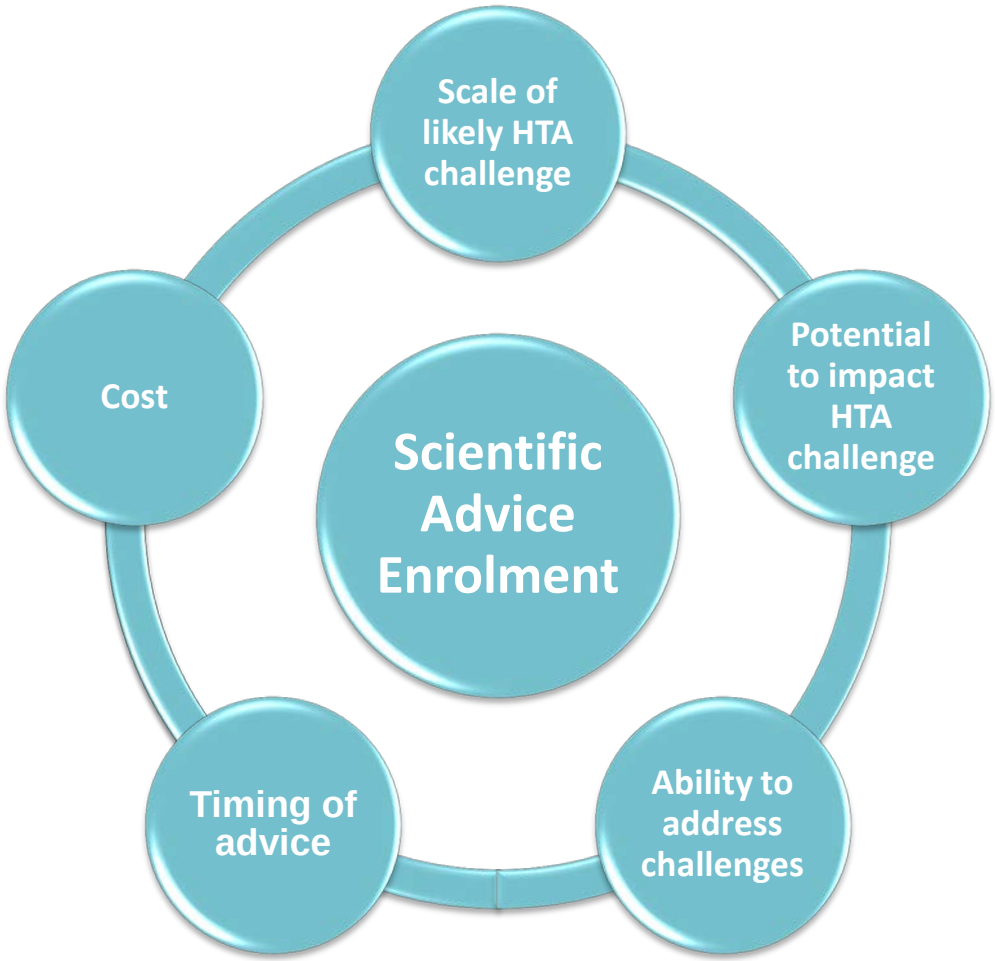
- HTA advice should be conducted as early as pre-Phase 2
  - PROs need time to develop and advice at Phase 3 is often too late
  - There is less time to adapt to HTA needs if advice is delayed
  - In oncology and other specialty diseases, Phase 2 studies are often pivotal

International Scientific Advice Programs[1]

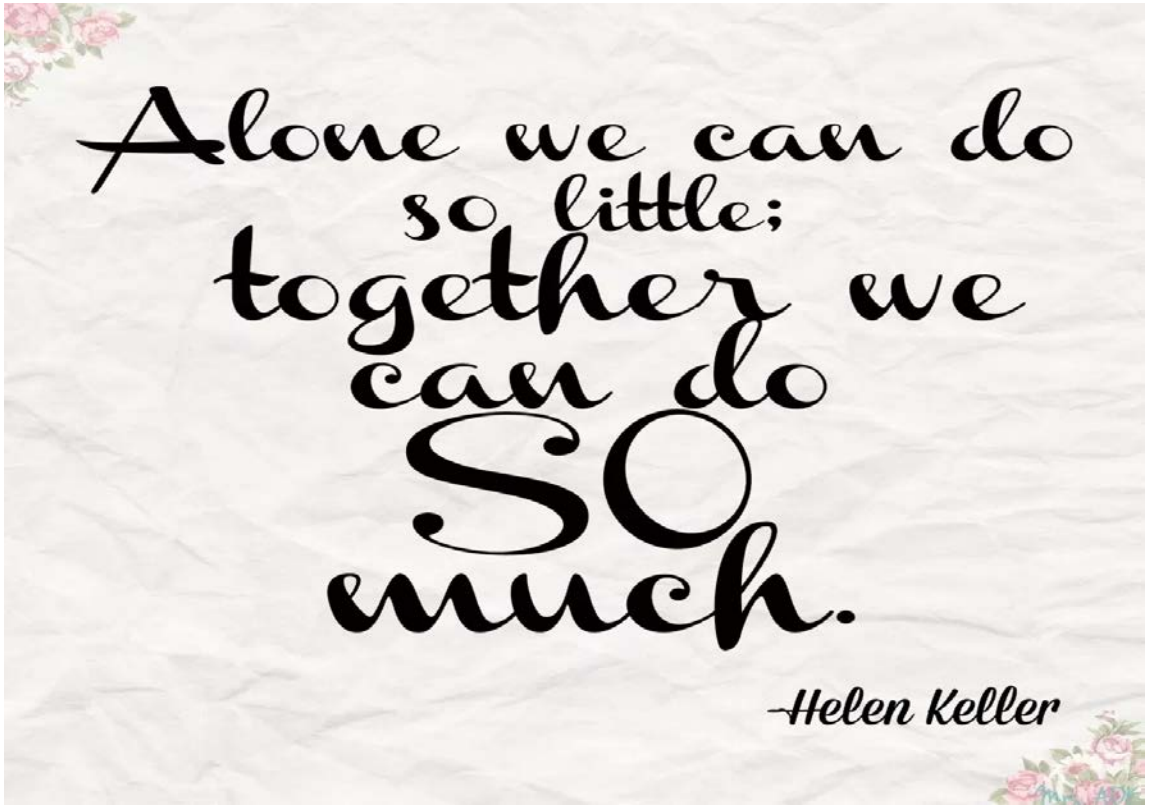
International/Non-governmental	Year of inception
• Tapestry	2010 (now closed)
• Green Park Collaborative International	2011
• IMI (Innovative Medicines Initiative, an EU Public-Private partnership)	2015
Europe	
- United Kingdom (NICE)	2009
- Sweden (TLV-MPA)	2009
- Netherlands (ZINL, ZINL-CEB)	Tapestry: 2010 then EUnetHTA
- Spain (Regional)	2010
- Italy (AIFA)	2011
- EUnetHTA pilots	2011-2015
- Germany (GBA)	2012
- France (HAS)	2012
- European Commission	2014
North America	
- FDA/CMS Parallel Review	2010
- Green Park Collaborative (USA)	2011
- MaRS EXCITE (Canada)	2011
- Canada (CADTH)	2015

1. Sood, A. Husereau, D., Blaney, L., Remillard, M., and Dempster, B. "Exploring Canada's early scientific advice: Global and Canadian context, CADTH and Health Canada Perspectives." Panel session presented at CAHR, October (2017).

Factors to consider when pursuing scientific advice – Global perspective



Why seek scientific advice?



CADTH Scientific Advice

Early Scientific Advice at CADTH

Amy Sood, PharmD
Manager, Scientific Advice, CADTH
CAPT panel, October 22, 2018

CADTH

Overview of Drug Review in Canada

CADTH Scientific Advice

CADTH

International Landscape

HTA Scientific Advice Programs[1]

Geographic Region	Country / HTA Agency / Program	Year of Inception
Europe	United Kingdom (NICE)	2009
	Spain (Regional)	2010
	Sweden (TLV-MPA)	2009
	Germany (GBA)	2012
	Italy (AIFA)	2011
	France (HAS)	2012
	Netherlands (ZINL, ZINL-CEB)	Tapestry: 2010
	EUnetHTA pilots	2011-15
	European Commission	2014
North America	Canada (CADTH)	2015
	Green Park Collaborative (USA)	2011
	MaRS EXCITE (Canada)	2011

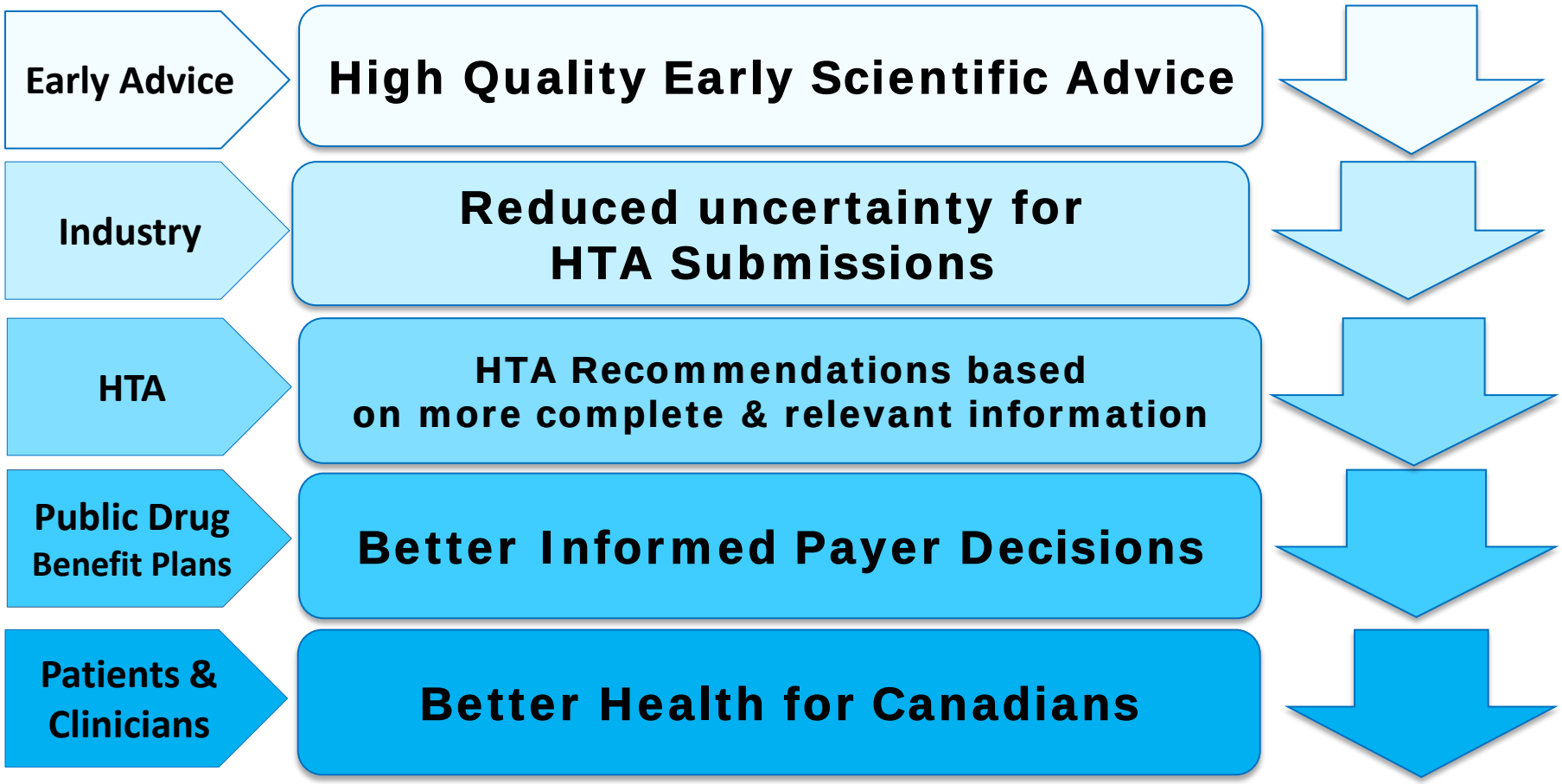
Early Parallel Scientific Advice

Geographic Region	HTA Agency / Regulatory Body	Year
Europe	EMA-EUnetHTA	July 2017[2]
UK	NICE-MHRA	2010[3,4]
Australia	PBAC-TGA (pilot)	May 2009[5]

References

1. http://pharmaphorum.com/views-and-analysis/needs-early-advice/
2. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001857.jsp&mid=WC0b01ac0580a11c96
3. https://www.nice.org.uk/about/what-we-do/scientific-advice/nice-mhra-scientific-advice
4. Wonder. Expert Rev Pharmacoecon & Outcomes Res 2014;4:465-7.
5. Wonder et al. Value in Health 2013;16:1067-73.

Potential Benefits for Stakeholders



CADTH Scientific Advice

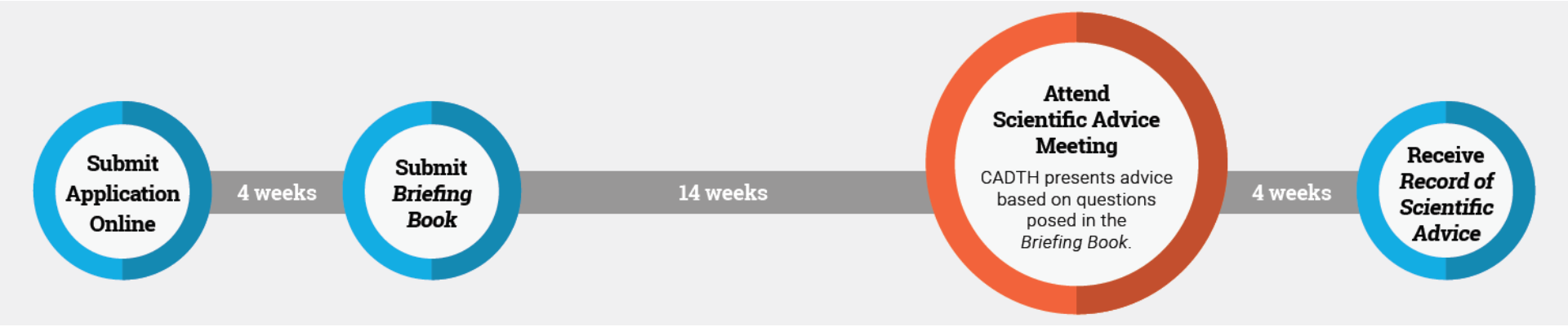
CADTH

Early Scientific Advice at CADTH

- Launched in January 2015
- Advice on early drug development plans from a Health Technology Assessment perspective, with emphasis on the Canadian setting
- Voluntary, non-binding, fee for service, cost-recovery program
- Eligibility: Prior to initiation of pivotal trials (Phase II or Phase III)

CADTH Scientific Advice Timelines

Standard Timelines

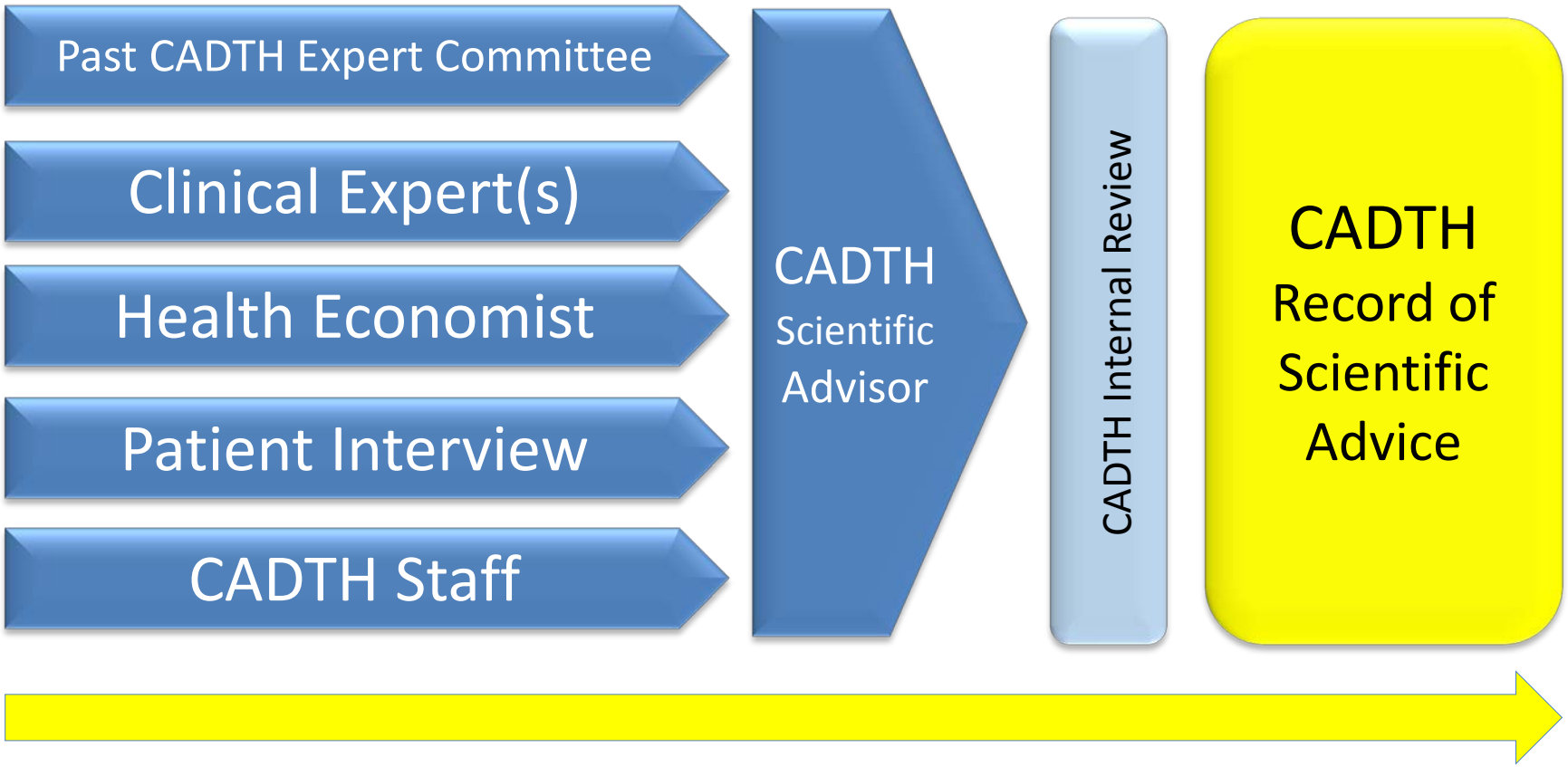


**Flexibility and customized timelines available*

CADTH Scientific Advice

CADTH

CADTH Record of Scientific Advice



Patient Involvement in CADTH Scientific Advice Process

- Individual patient with the condition is invited to an interview:
  - *Patient journey from diagnosis, symptoms over time*
  - *Treatment experiences, challenges*
  - *Most significant health issues related to the condition that impact daily life*
  - *What is hoped for in a new treatment*
- Patient interview summary and key points from past patient group input provided to the company and incorporated into the advice

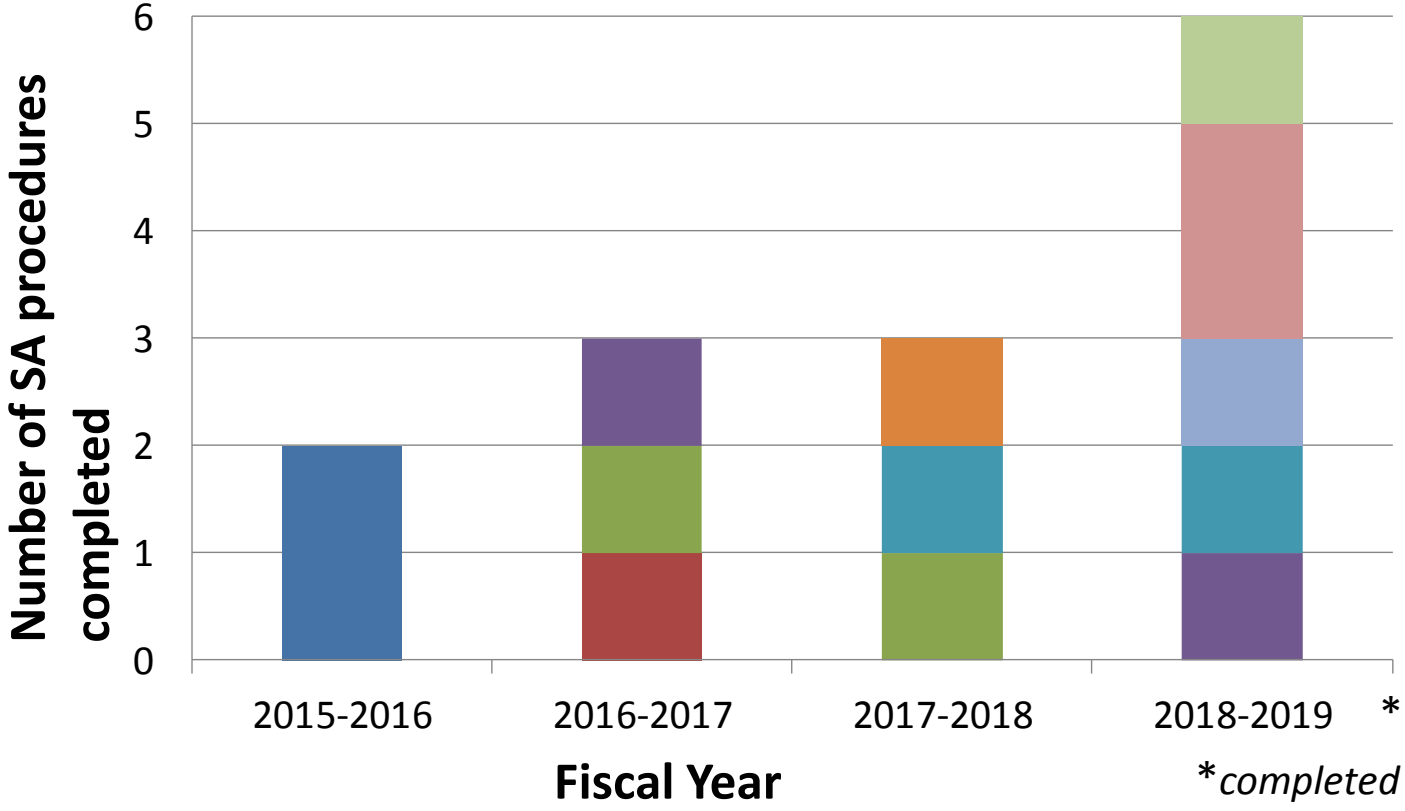
Types of Advice Requested

Clinical Trial Design	Economic Analysis
Target trial population and subgroups	Population(s)
Trial Design and duration	Choice of comparators
Choice of trial comparators	Choice of economic model
Primary and secondary endpoints; surrogate outcomes	Data to populate the model
Patient-reported outcomes	Utility values
Health-related quality of life measures	Time horizon and extrapolation hypotheses
	Resource utilization data

Early Scientific Advice on Real World Evidence Generation?

- Early scientific advice has a potential role for providing the HTA perspective on whether proposed plans for RWE generation may support the clinical development program
- As this space continues to evolve, there may potentially be a larger role for Scientific Advice in providing advice on RWE

CADTH Scientific Advice Experience To Date



Among 14 SA Procedures, 5 companies each returned a second time

**completed or in progress*

CADTH Scientific Advice

CADTH

Evaluating Outcomes of the Program

To be undertaken, once a number of applications that have been through early advice procedures return to CADTH for assessment

Outcomes of interest:

- Early advice incorporation into the clinical development plan
- Early advice and outcome of reimbursement recommendation

CADTH/NICE
Parallel Scientific Advice

- Parallel procedure *in progress* with NICE Scientific Advice (UK)
- Joint Scientific Advice Meeting with CADTH/NICE/company held
- Preliminary process; further details will be available later in the year

- Interested companies can contact either CADTH or NICE:
  - scientificadvice@cadth.ca
  - scientificadvice@nice.org.uk

CADTH Scientific Advice

CADTH

Future of Scientific Advice in Canada

- Exploring CADTH / Health Canada Parallel Scientific Advice
- Opportunity for companies to discuss any divergent advice in real time between regulator and HTA in Canada
- Updates to be provided

CADTH Scientific Advice

Thank you

scientificadvice@cadth.ca

cadth.ca/scientific-advice

@cadth_acmts

CADTH Evidence Driven.
ACMTS Preuves à l'appui.

Health Canada Santé Canada

Canada

Early Scientific Advice at Health Canada

CAPT panel discussion
October, 2018

megan.bettle@canada.ca

YOUR HEALTH AND SAFETY... OUR PRIORITY.

Issue – International Filing Strategies

The drugs come…

- In 2016, Canada approved 33 new active substances (NAS)
  - 60% followed an accelerated review pathway (priority review or conditional authorization)

- 15 of these products are considered “orphan” drugs by EMA or FDA
- Median approval time is similar to other big regulators

…but they don’t come to Canada first:

- 85% of the NAS approved by HC in 2016 were approved by other regulators first (generally FDA and EMA)

- Median submission gap was ~ 6 months

(data from http://www.cirsci.org/wp-content/uploads/2017/11/CIRS-RD-Briefing-65-20112017.pdf)

Current Health Canada Advice Processes
(Not cost-recovered)

Pre-Clinical Trial Application meetings

- Advice for clinical trials (phase I/II/III) which will be conducted in Canada
- Generally responsive – ie, comments on a trial proposal, rather than advice to support *de novo* trial planning
- Focus on regulatory advice, especially for academics, small companies – ***how*** to do it, not ***what*** to do

Pre-submission meetings

- Generally used as pre-filing meetings - phase III trials are done or almost completed, focus is on presenting data and how submission will be structured
- Rarely early enough to influence drug development pathway
- Limited capacity – cannot accommodate all requests
  - Work in progress to better define criteria for accepting meetings and to streamline processes to make them more efficient

If you build it, will they come? (1)

Consultation on early advice held in late 2017

- Larger brand name companies confirmed that their focus is on requirements for larger markets (EMA/FDA)
- Generic companies suggested early advice would be valuable to support development plans
- Companies with products which might qualify for accelerated review pathways see benefit in early interactions and feedback
- Advice given in parallel with HTA organizations seen as valuable, if it didn't increase burden
- In theory, stakeholders think early advice could lead to more efficient regulatory reviews and higher quality submissions

If you build it, will they come? (2)

Health Canada pilot project – scientific advice for biosimilars

- Launched in 2015 as a 3 year pilot
- Established process to request an early meeting to discuss acceptance of a development plan for a drug to be considered as a biosimilar
- As of Fall 2018….

..... no meetings have been requested

- But multiple drugs have still been approved as biosimilars

Health Canada's Plan for Transformation

- **Objective: An agile regulatory system that supports better access to therapeutic products based on healthcare system needs**

Expanded collaboration with health partners

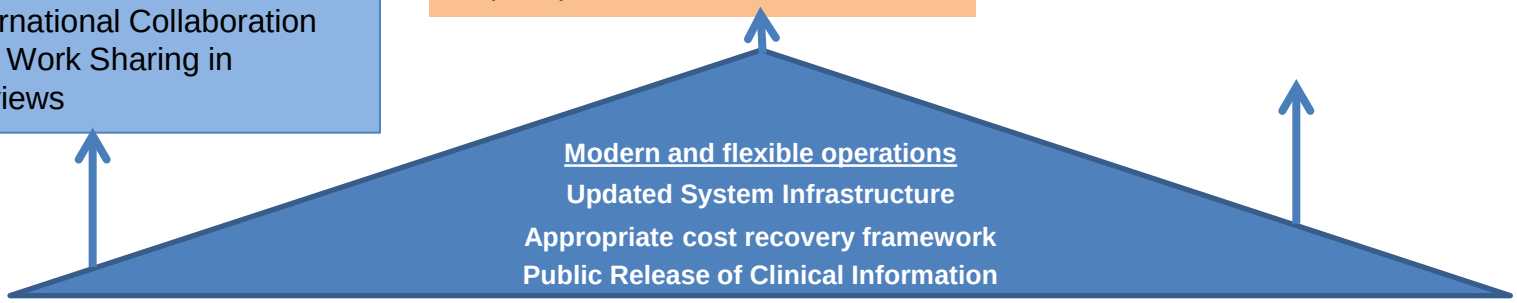
- Alignment of the Health Technology Assessment (CADTH) Review with Health Canada Review
- **Implementing a Mechanism for Early Parallel Scientific Advice**
- Use of Foreign Reviews/Decisions
- International Collaboration and Work Sharing in Reviews

More timely access to drugs and devices

- Expansion of Priority Review Pathways
- Improving Access to Biosimilars and Biologics
- Improving Access to Generic Drugs
- Building Better Access to Digital Health Technologies
- Pre-Submission Scientific Advice for Medical Devices
- Special Access Programme (SAP) Renewal

Enhanced Use of real world evidence

- Leveraging Data for Assessing Drug Safety and Effectiveness
- Strengthening the use of real world evidence and regulations for medical devices



What is EPSA?

- **Early** - given at a point in time in drug development which is early enough to influence the development of critical trials
  - Generally, before Phase III pivotal trials are finalized

- **Parallel** – involving both the regulator and the health technology assessment organization
  - With the aim of supporting drug submissions that will best meet the needs of both regulator and HTA, increasing alignment across these two decision-making steps

- **Scientific** - clinical, technical or regulatory advice, e.g. on:
  - Trial design and endpoints
  - Best regulatory pathway
  - Data requirements

International Context

- The European Medicines Agency (EMA) and the European Network for Health Technology Assessment (EUnetHTA) have established a program in 2017, following a pilot phase.

- Parallel process aims to allow medicine developers to obtain non-binding feedback from regulators and health technology assessment (HTA) organizations on their evidence-generation plans to support decision-making on marketing authorization and reimbursement of new medicines at the same time.

- FDA does provide extensive advice alone in certain accelerated pathways, but does not currently provide advice in parallel with any US HTA organization

CADTH's current early advice program

- Structured program to offer early advice from Canadian HTA perspective
- Voluntary, non-binding
- Fee-for service, cost-recovered
- Fire wall – between CADTH team (internal staff + external experts) involved in early advice and CADTH expert committees involved in later review
- HC reviewers have been attending CADTH advice meetings as observers for past year, ~ 5 processes completed

Proposal for a quick win and path forwards

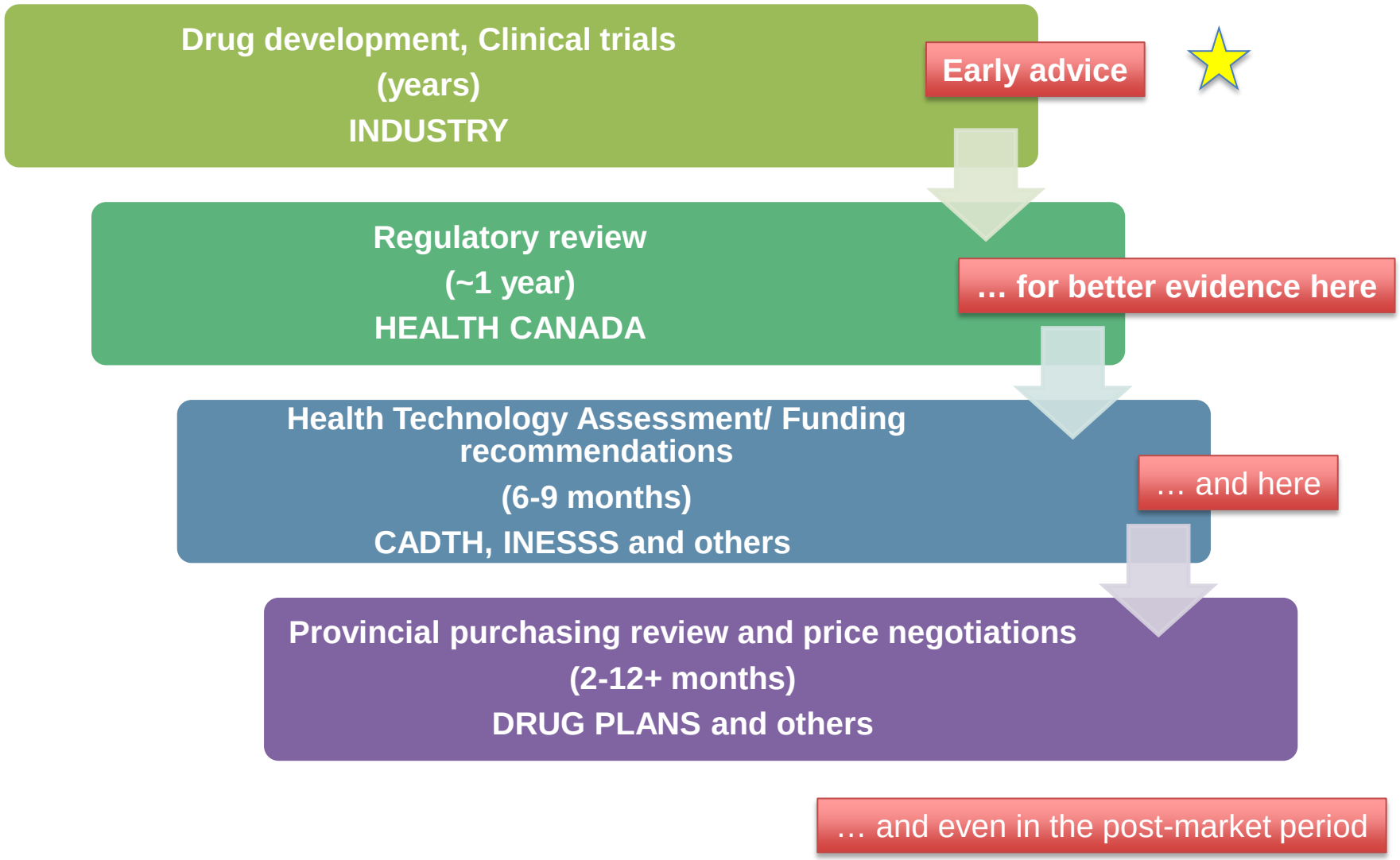
- Build on CADTH's existing process to add active HC involvement throughout to provide advice from the regulator's perspective
  - Pilot project to be initiated from Fall 2018

- At this time, sponsor would need to pay CADTH's fee, but additional HC advice would not currently cost more
  - Briefing package and questions would be submitted to both partners
  - Both would participate equally

- Advice would be non-binding, and parallel – in that CADTH and HC would respond to questions independently, but:
  - HC staff would gain from discussions with independent clinical experts and from receiving patient perspective
  - HC and CADTH would have opportunities to discuss responses, and either align or document why advice may be different

Proposal for a quick win and path forwards (2)

- Internal processes have been mapped, and process changes are being finalized to allow implementation
- Candidates are being sought for pilot project of parallel advice
- After several advice sessions have been completed, feedback from participants (industry and staff) would be sought, and process improvements made as needed
- Future state could also include HC-only or HC-foreign regulators early advice pathways


Drug development, Clinical trials
(years)
INDUSTRY
Early advice
Regulatory review
(~1 year)
HEALTH CANADA
… for better evidence here
Health Technology Assessment/ Funding recommendations
(6-9 months)
CADTH, INESSS and others
… and here
Provincial purchasing review and price negotiations
(2-12+ months)
DRUG PLANS and others
… and even in the post-market period

R2D2 Webpage and Consultations

- Dedicated webpage includes project summaries, timelines and upcoming opportunities for consultation

- Webpage is being updated regularly, providing a single point of contact for the initiative

https://www.canada.ca/en/health-canada/corporate/transparency/regulatory-transparency-and-openness/improving-review-drugs-devices.html

Getting Scientific Advice:

Considerations for Real World Evidence (RWE)

Muhammad Mamdani, PharmD, MA, MPH

Director – Li Ka Shing Centre for Healthcare Analytics Research and Training (LKS-CHART) of St. Michael's Hospital

Professor – University of Toronto

October 2018

Real World Evidence – What Is It?

Real World Evidence – What Is It?

- Wikipedia (accessed September 2018)
  - evidence obtained from real world data (RWD), which are observational data obtained outside the context of randomized controlled trials (RCTs) and generated during routine clinical practice.

- US Food and Drug Administration (Sherman et al, NEJM 2018)
  - the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real world data (e.g. electronic health data, claims data, registry data, data from mobile device)

- Practical Definition (some random person)
  - Evidence that reflects 'real world' healthcare services and policy constraints, clinical practice, and patient behaviours

The Tension Between Traditional Clinical Trials and RWE

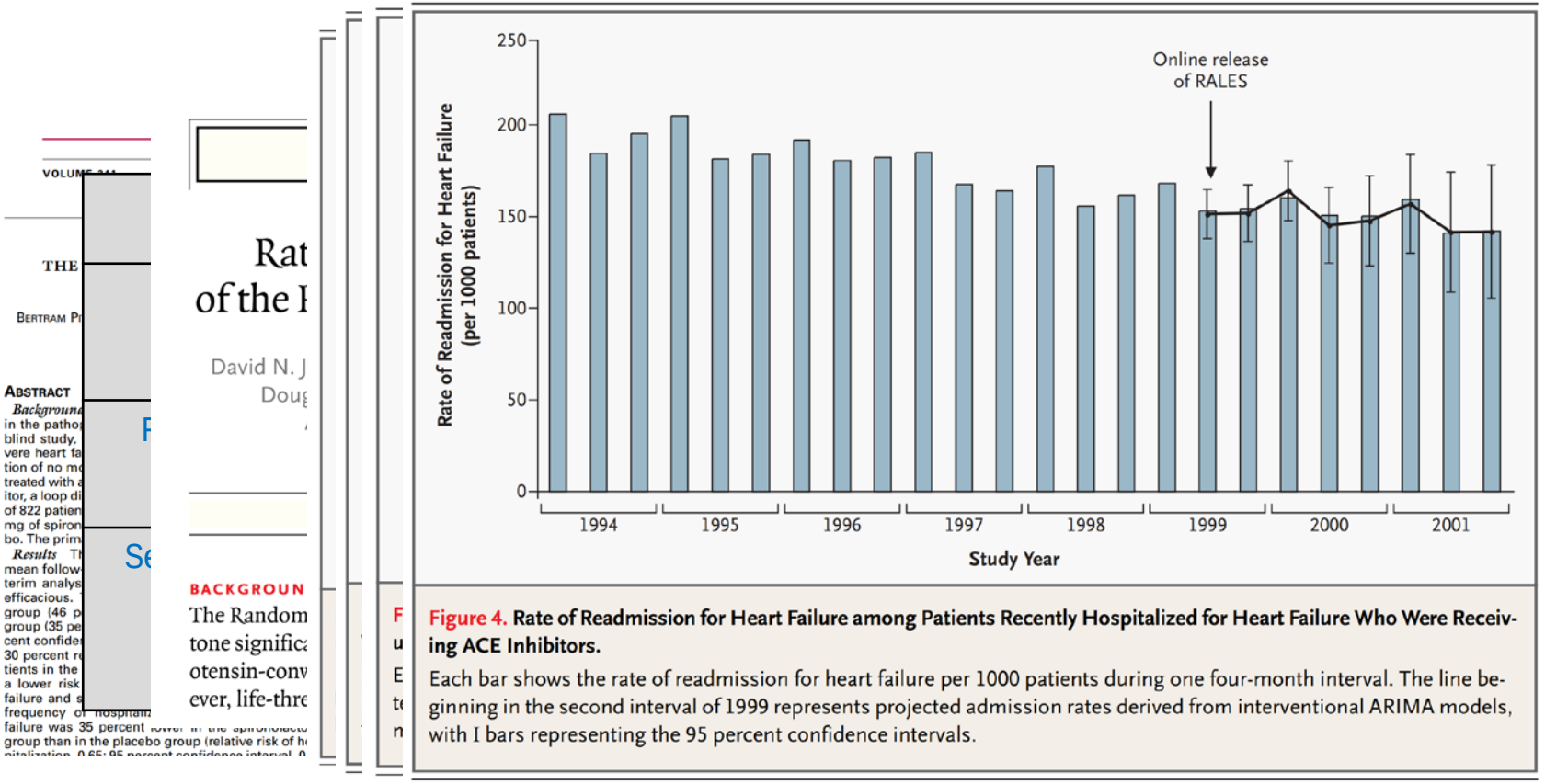


Figure 4. Rate of Readmission for Heart Failure among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the rate of readmission for heart failure per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 represents projected admission rates derived from interventional ARIMA models, with I bars representing the 95 percent confidence intervals.

Scientific Advice As it Relates to RWE

- **Perspective drives everything**
  - Must keep the end-user in mind: will drive study design, choice of outcomes, etc
  - Alignment/engagement with HTA bodies vs. payers?

- **Requires methodological expertise**
  - Lots of approaches to choose from!
  - Study design and statistical analysis expertise become important

- **Timelines and accessibility need to be considered**
  - Start planning early
  - Can't study 'actual' use and outcomes of something that isn't available/accessible – progressive listing opportunities?

- **External collaborations**
  - Example: third-party evaluators?

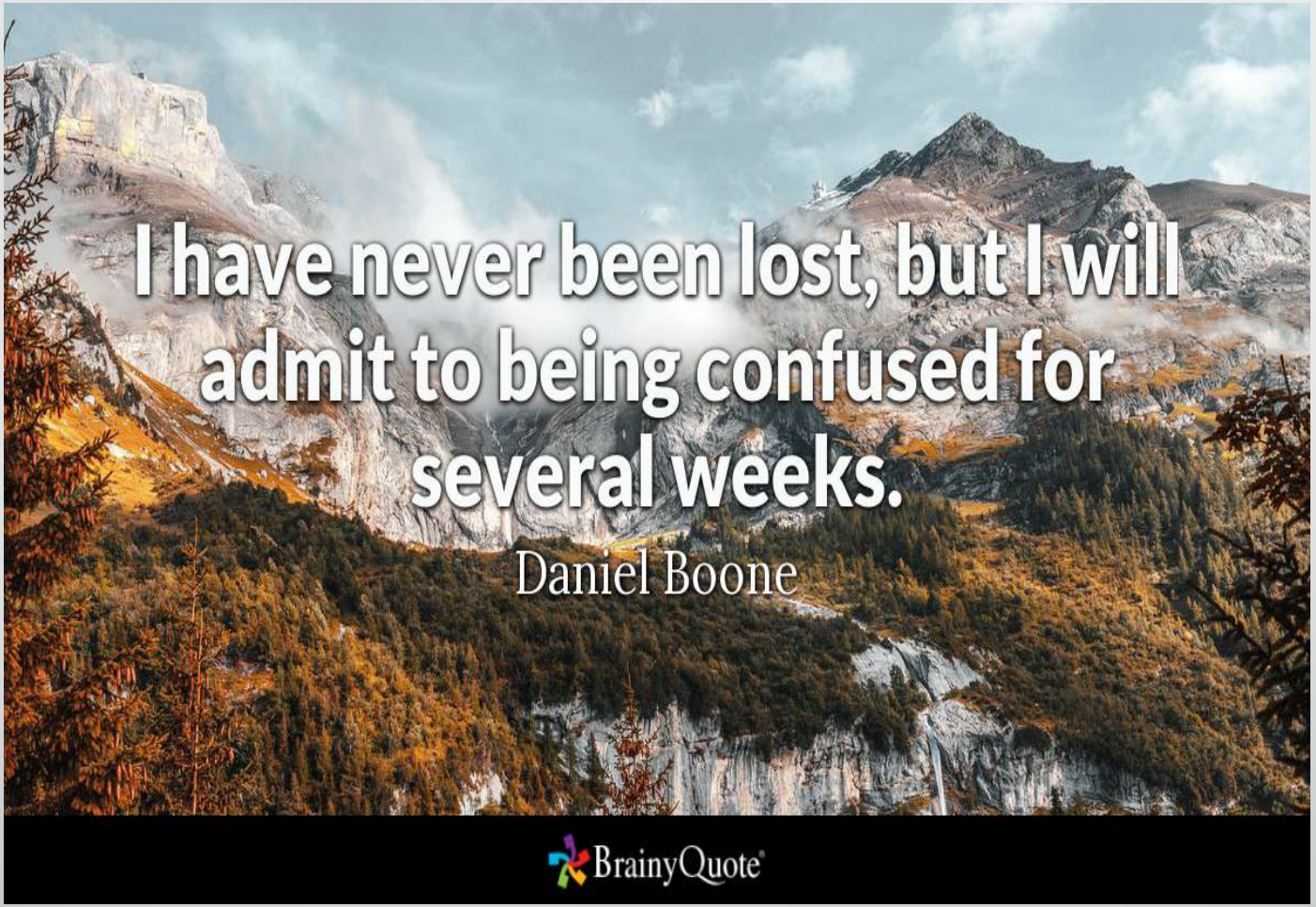
Early Scientific Advice
What do Funders think about?

CAPT Panel – October 22, 2018

Suzanne McGurn

The Challenge

What is the "right evidence" to inform the decision to publicly fund?


I have never been lost, but I will admit to being confused for several weeks.
Daniel Boone
BrainyQuote

Tough Choices

Don't require less evidence,
but they may require different evidence….

So what do we think about?

- How well does it work
  - Compared to placebo?
  - Compared to current treatments – drug/other?
- End-points chosen
  - Do they matter to patients?
  - Do they matter to clinicians?
  - Do they impact the health (or other) systems?
- Length of research
  - Initial response vs. sustained response
- Do we understand the research in the same way?
- Standardization & Agility
  - Similar concerns are being identified by other international jurisdictions - are there opportunities for better alignment
- Are there hidden agendas in the approach to research?
- Are we all in this for to make it better for all of us? Or just some of us?

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