ARCC
Canadian Centre
for Applied Research
in Cancer Control

Are We Ready for RWE: What do We Need to Create RWE from a Technical Perspective?

CAPT 2018

Wanrudee Isaranuwatchai, PhD

23 October 2018

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Are We Ready for RWE?

From Various Perspectives

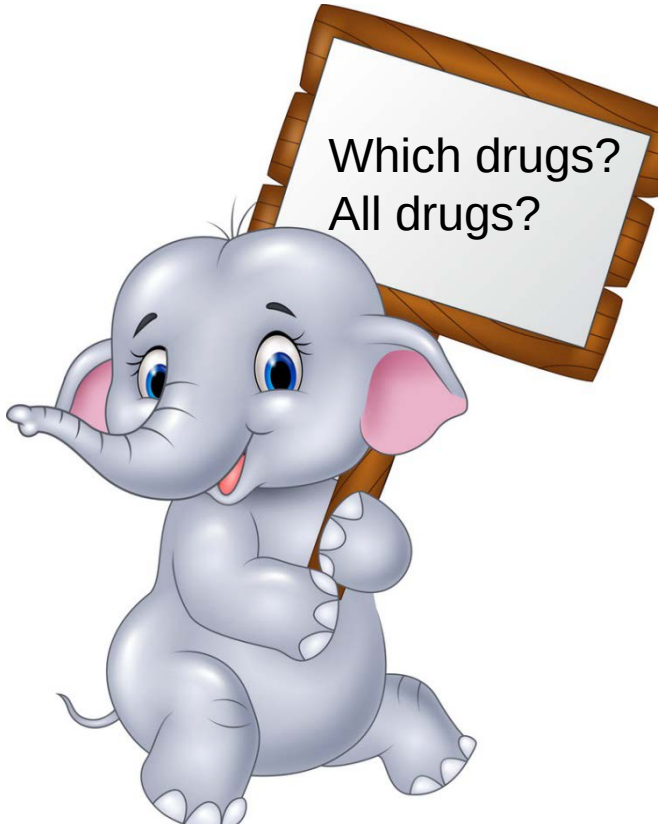
RWE is here to stay

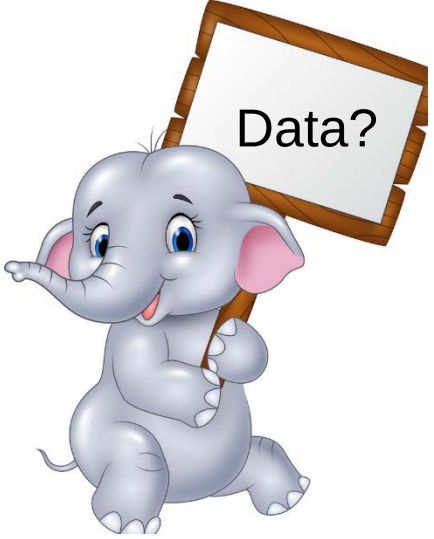
Nothing should stop RWE

Can we do more RWE in Canada? We can and we are...

The train has left the station (x2)


Who to conduct the analysis?


Which drugs? All drugs?


Data?


How should RWE be used or reviewed?

Today

- Are we ready for RWE?
- What do we need to support RWE?

Charles Victor

- Senior Director, Strategic Partnerships and External Services, ICES
- Assistant professor, University of Toronto

Are we ready for RWE: Do we have the systems in place to enable RWE

A PERSPECTIVE

J. CHARLES VICTOR, MSC, PSTAT
SENIOR DIRECTOR, STRATEGIC PARTNERSHIPS AND EXTERNAL SERVICES
ICES

Do we have the systems in place to enable RWE

System comprises multiple factors

- Subject matter support system
- Technical infrastructure
- Legislative and regulatory framework

Scope matters…. What is required for RWE?

- Any data (globally)?
- Any data within Canada? IE provincial data
- Pan-Canadian Data

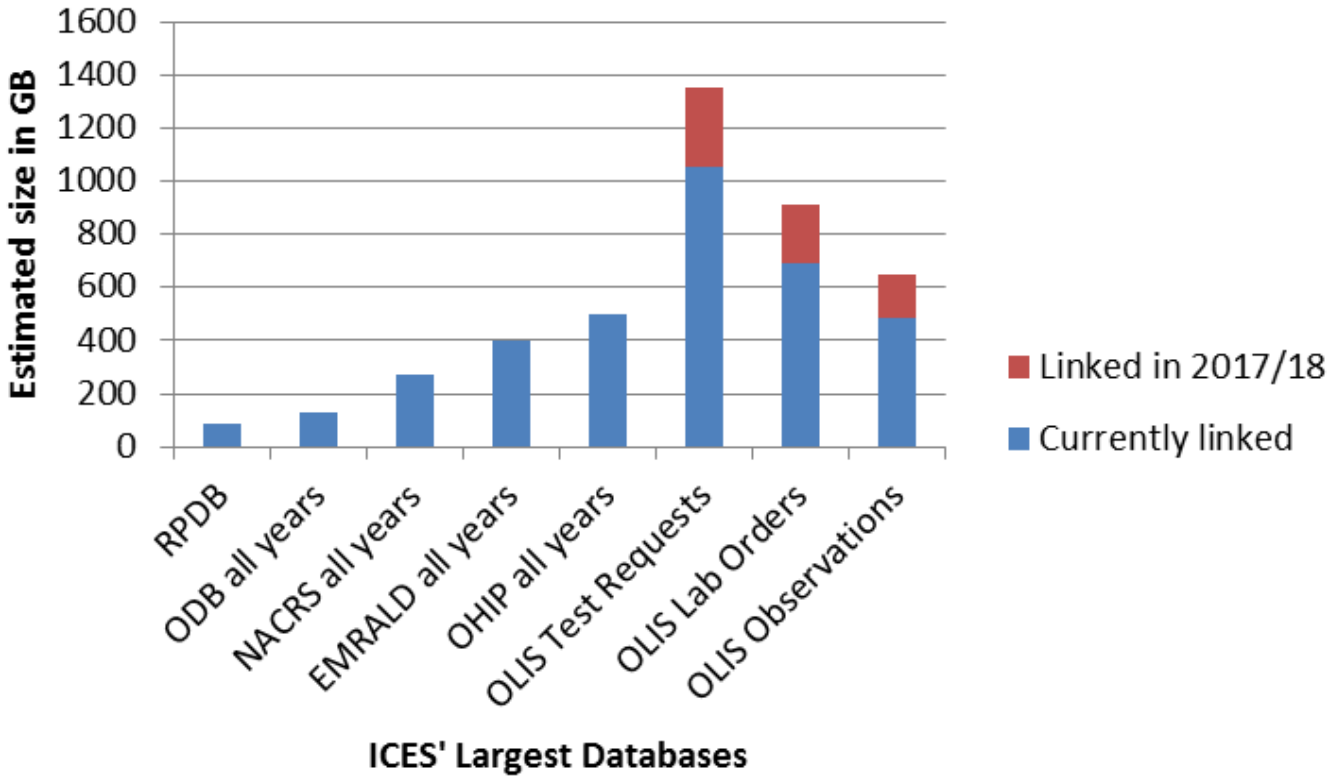
Do we have the….. Subject and Technical infrastructure?

Yes and no

- Pockets of exemplary infrastructure nationally
    - ON, BC, MB have mature internal and external (ON, BC) researcher access models
    - AB to have a fully integrated model for internal research
    - StatsCan and CIHI developing pan-Canadian models

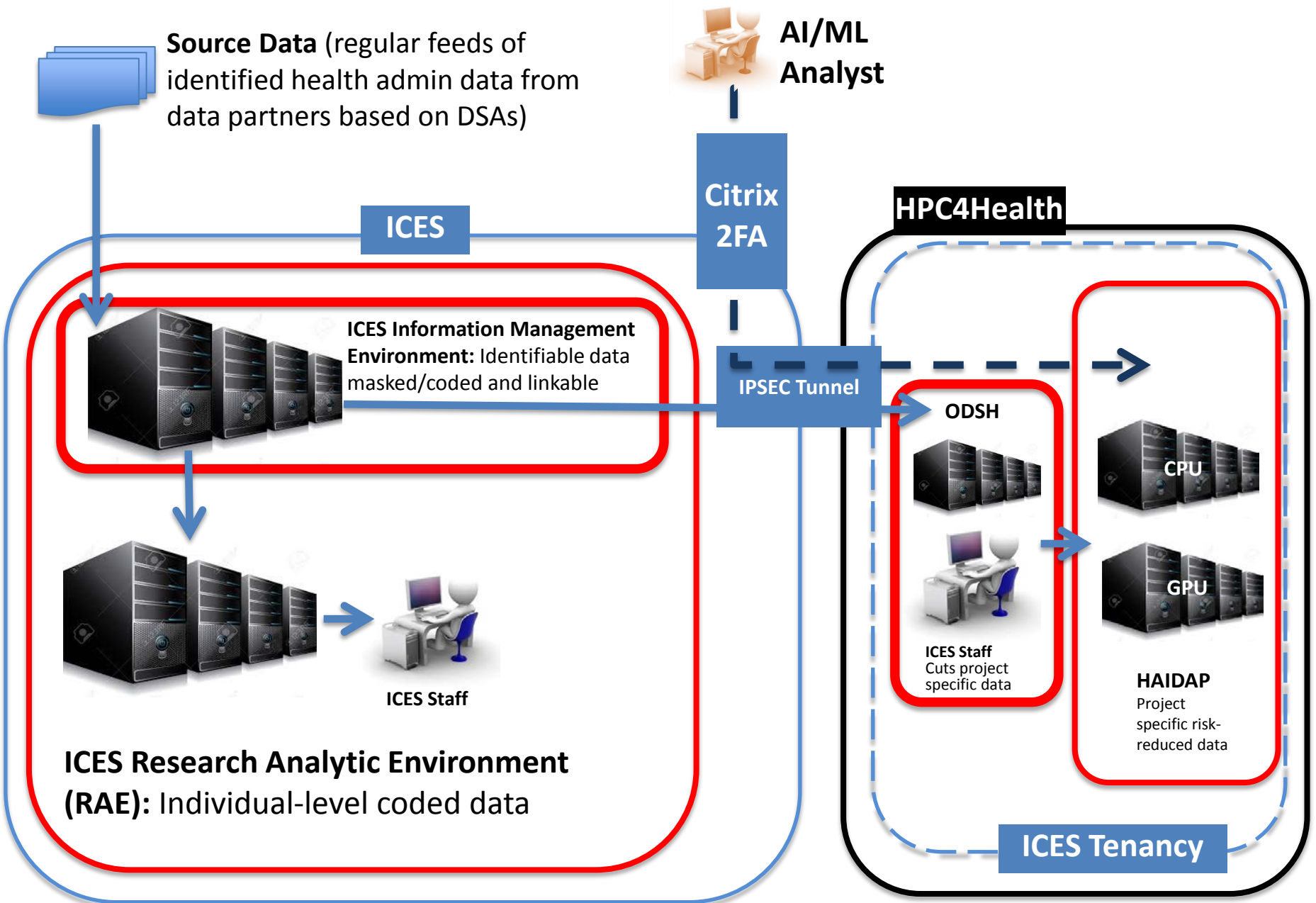
Challenges keeping up with current trends

- Increasing demand on IT services related to provincial repositories
- EG at ICES:
    - Data repository size increases (lab values doubled repository size)
    - Complexity of data schemas increases (e.g., OLIS, Cerner)
    - Increased number data assets dependent on free text fields (e.g., EMRALD)
    - Scientists requesting to bring in ‘omics data (e.g., whole genomes) to link to outcome data
    - Increased demand from ICES scientists and non-ICES scientists for novel and advanced analytic techniques
        - Social network analysis
        - Neural networks (AI)
        - Natural language processing of free-text medical records
        - GWAS analyses
- Provincially-funded repositories do not have the human or financial resources to develop and maintain a stand-alone high performance computing environment



RPDB: Registered Person's Database
ODB: Ontario Drug Benefit
NACRS: National Ambulatory Care Reporting System
OHIP: Ontario Health Insurance Plan
EMRALD: Electronic Medical Record Administrative data Linked Database
OLIS: Ontario Laboratory Information System

ICES Data Flow: ODSH & HAIDAP

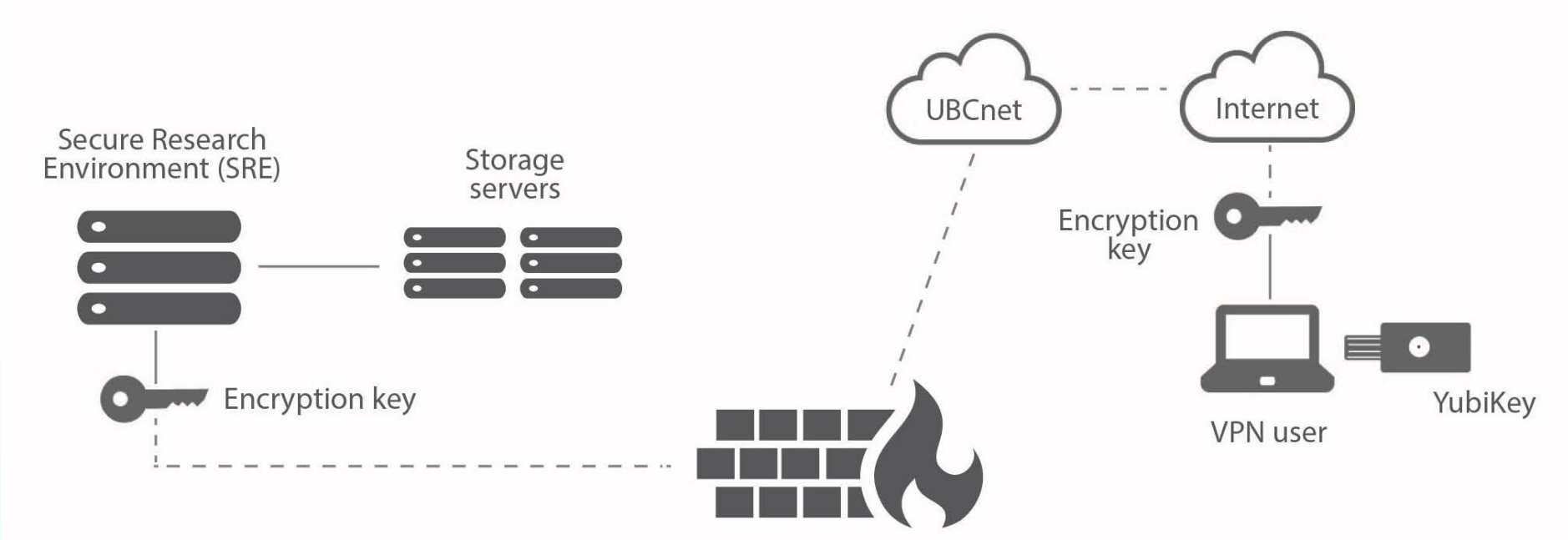


A resource for complex health analytics

	ICES RAE	ODSH*	HAIDAP*
Annual Analytic Projects	300-500		
CPU Cores	80	120	400+
GPU Clusters	1 (<100TFLOPS)	0	13 (up to 1.26 PFLOPS)
Storage	200 TB	2+ PB (est)	

*Numbers are estimates

PopData BC: Secure Research Environment



Do we have the….. Legislative and Regulatory Framework?

Yes and no

- Within province systems exist for most provinces
    - More cumbersome in some provinces compared to others
        - EG authority of data access a single unit vs researcher seeking data sharing agreements with each data source

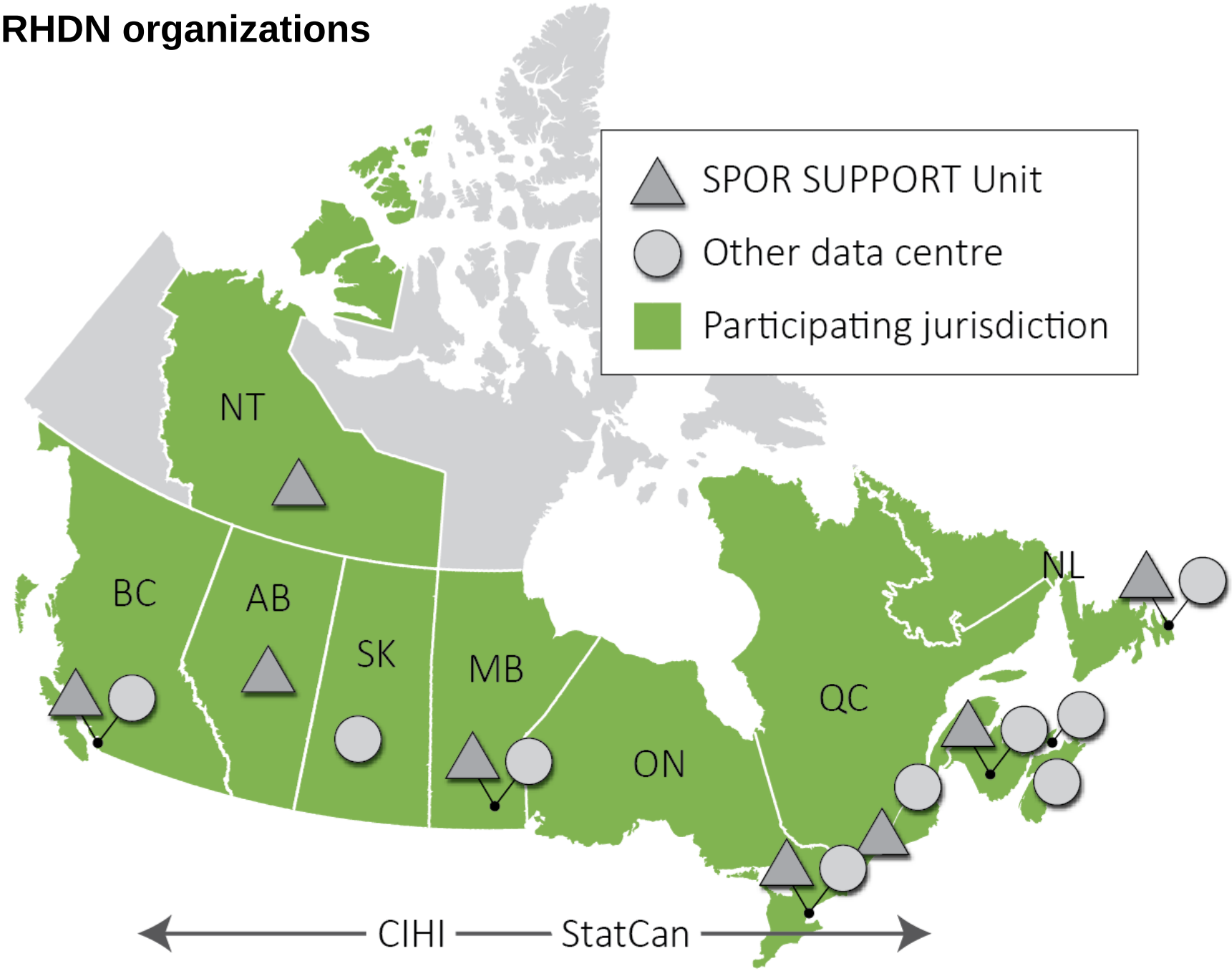
Challenges combining (administrative) data across jurisdictions

- Many/most provinces require legislative change prior to administrative data allowed to cross provincial borders
    - Impairs ability to promote/analyse harmonised definitions of factors/outcomes

- Some current success stories
    - CNODES: Canadian Network for Observational Drug Effect Studies

- Some future success stories
    - PRHDN: Pan-Canadian Real World Health Data Network

PRHDN organizations



Bottom line……

Do we have the systems in place to enable RWE

- We are almost there…..
- Poised to be the most valuable centres for true RWE
  - Population-wide coverage
  - Limited sampling bias
  - Strong hx and expertise in health services research

Dr. Claire de Oliveira

- Health Economist, CAMH
- Assistant Professor, U of T
- Adjunct Scientist, ICES
- Expert Lead in cancer economics, CPAC
- Associate Member and Co-Program Lead for HTA, ARCC
- Collaborator, THETA

Are We Ready for RWE: What do we need to create RWE from a technical perspective?

Claire de Oliveira, M.A., Ph.D

camh
Centre for Addiction and Mental Health
Centre de toxicomanie et de santé mentale

Introduction

What is real world evidence?

- "real world evidence (RWE) in medicine means 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."
- "RWE is generated by analysing **data** which is stored in electronic health records (EHR), billing activities databases, registries, patient-generated data, mobile devices, etc."

- availability of real world data can generate valuable real world evidence (RWE) for many stakeholders to make evidence based decisions.
- take-home message: to undertake RWE, we need **DATA**

Introduction

Are we ready to undertake RWE in Canada from a data perspective?

- short answer: YES

- but… with caveats
- what are some things to think about?

What do we need?

Data Sources

- health care records collected through administration of provincial/territorial public health insurance plans
  - British Columbia: PopulationData British Columbia
  - Manitoba: Manitoba Population Research Data Repository
  - Ontario: ICES
  - Newfoundland and Labrador: Newfoundland and Labrador Centre for Health Information

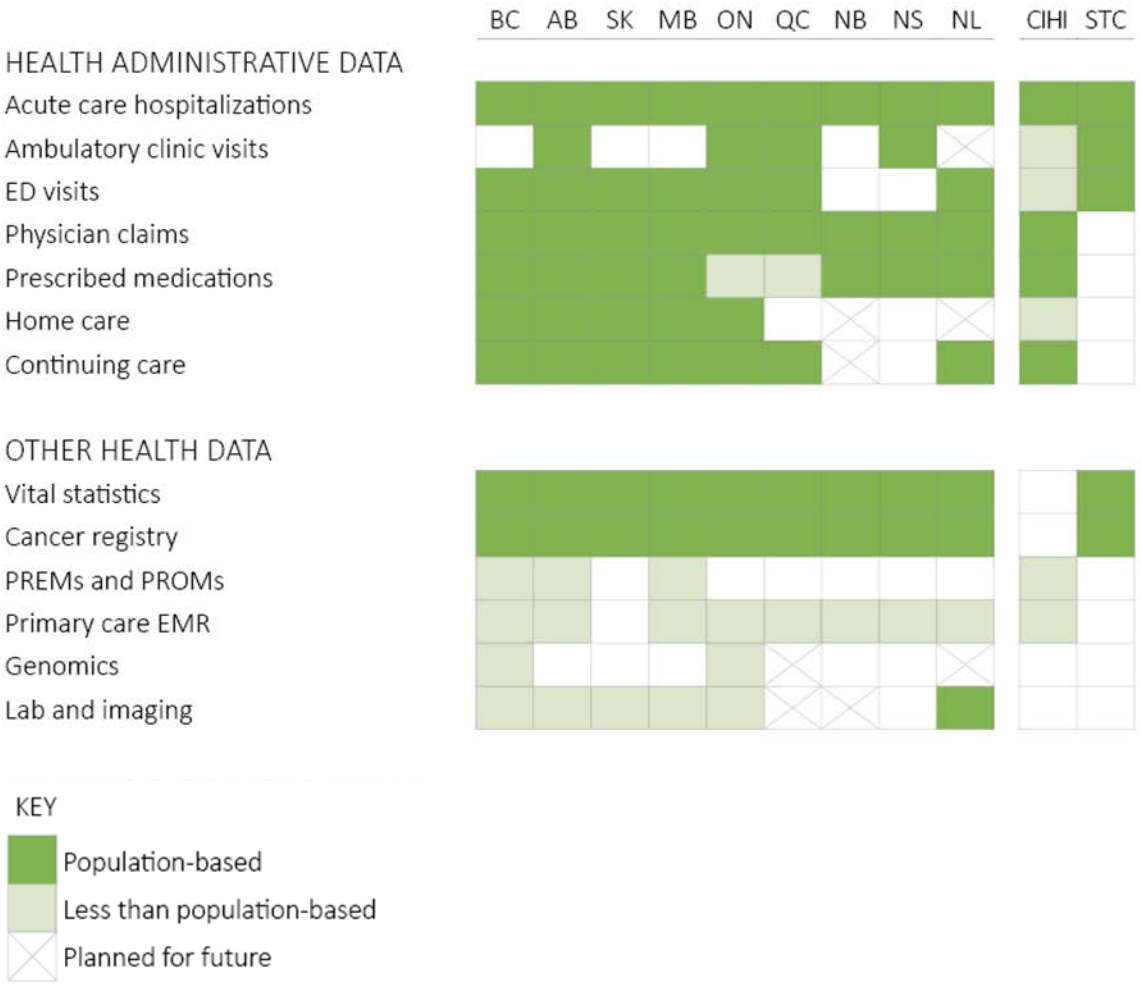
What do we need?

Data Sources

- disease-specific registries
  - cancer registries
  - Canadian Organ Replacement Register
- treatment data
  - chemotherapy
  - radiation therapy
- hospital records/data
  - Edmonton Symptom Assessment Scale (ESAS) scores

What do we need?

Data Sources



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What do we need?

Example applied to cancer treatment data

Analysis	BC	AB	SK	MB	ON	QB	NS	NB	NFL	PEI
Systemic therapy (Y/N)										
Can distinguish IV vs PO										
Distinguish lines of systemic therapy										
Radiation therapy										
Surgery										

Data available and linkable

Data available and linkable with caveat

Data available and linkable with major caveat

Data not available or linkable

IV = Intravenous cancer drugs
PO = Take home oral drugs

Source: CanREValue PHSI grant

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What do we need to think about?

Pitfalls

- some data may not readily available → may need to obtain data from other sources outside of provincial data warehouses
  - e.g. treatment data from cancer agencies
- quality of some administrative/treatment data are not good
  - e.g. missing data, data reported for some years but not other years
- unit costs may not always be available in the data
  - unit costs in physician billings/drug data versus weighted average in CIHI data (don't have data on charges like the US)

What do we need to think about?

Pitfalls

- data availability/quality vary great across provinces → difficult to undertake pan-Canadian analyses
  - e.g. National Ambulatory Care Reporting System data: only Alberta and Ontario currently report these data for the full province (and only Ontario has data prior to 2010)
  - need to undertake data harmonisation
- inter-provincial analyses can be challenging
  - data typically cannot leave their jurisdiction
- relatively quick access to data can be an issue in some jurisdictions
  - can make it challenging to undertake current/up-to-date analyses
- expertise/capacity to undertake RWE analyses exist but also vary by province/territory (and some jurisdictions may have more capacity than others)
  - call for capacity building in the field

Concluding remarks

We are ready to undertake RWE

- Canada is well positioned to undertake RWE analyses
  - we have good data, we have expertise

But

- need to bear in mind data challenges
  - availability, quality
  - inter-provincial analyses; even intra-provincial analyses sometimes
  - data harmonisation
- and need to build capacity in some jurisdictions

Thank you.

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Dr. Jeffrey Hoch

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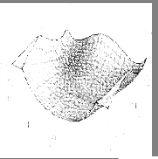
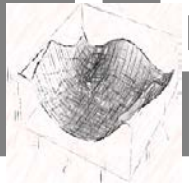
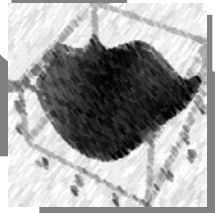
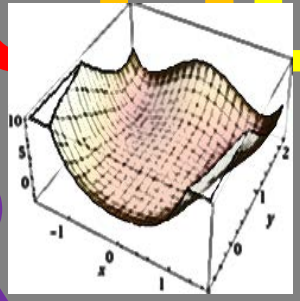
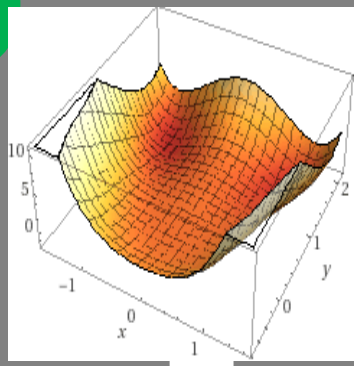
- Chief, Division of Health Policy and Management, University of California at Davis
- Associate Director, the Center for Healthcare Policy and Research, University of California at Davis
- Inaugural Director,

CONSIDERATIONS

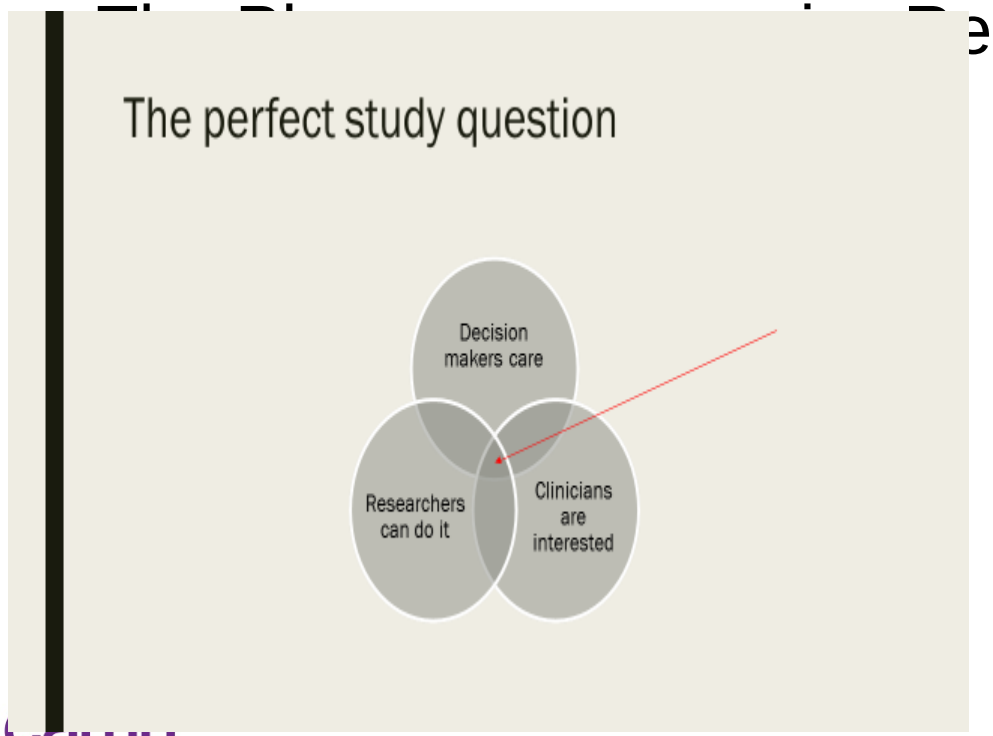
Jeffrey Hoch, PhD

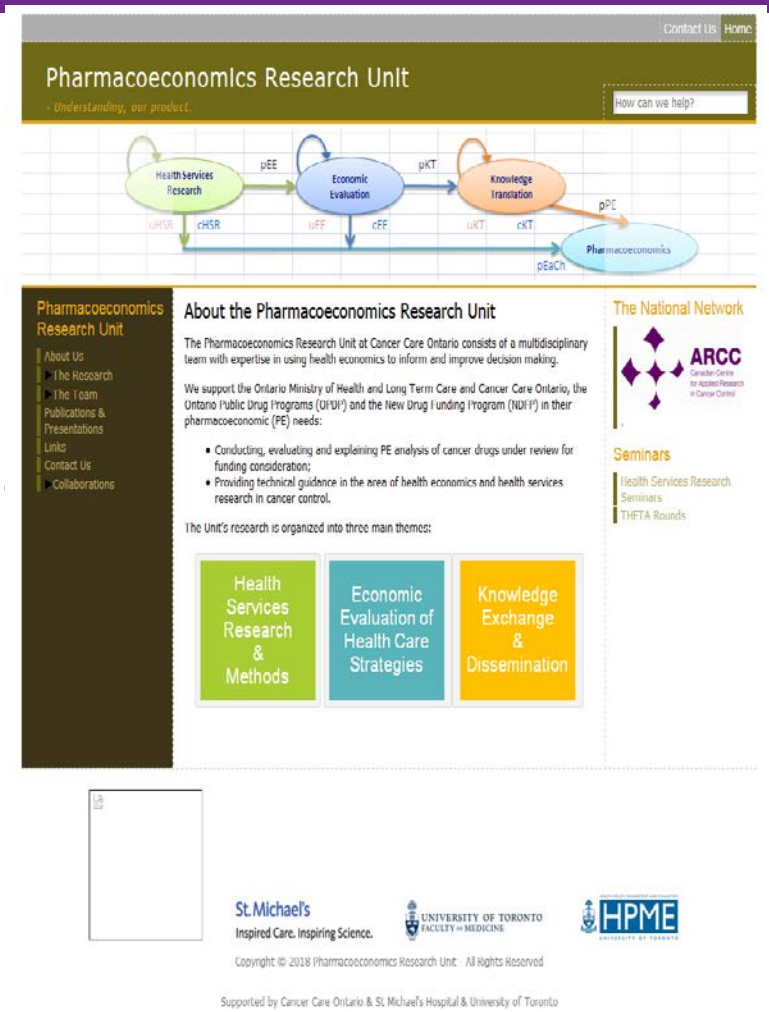
Professor and Chief ,
Division of Health Policy and Management,
Department of Public Health Sciences

Main points

- The “key” technical issues will change
- Things will not be 100% perfict
- Continued investment in the area is crucial

Background


The perfect study question
Decision makers care
Researchers can do it
Clinicians are interested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The Team
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About the Pharmacoeconomics Research Unit
The Pharmacoeconomics Research Unit at Cancer Care Ontario consists of a multidisciplinary team with expertise in using health economics to inform and improve decision making.
We support the Ontario Ministry of Health and Long Term Care and Cancer Care Ontario, the Ontario Public Drug Programs (OPDP) and the New Drug Funding Program (NDFP) in their pharmacoeconomic (PE) needs:
Conducting, evaluating and explaining PE analysis of cancer drugs under review for funding consideration;
Providing technical guidance in the area of health economics and health services research in cancer control.
The Unit's research is organized into three main themes:
Health Services Research & Methods
Economic Evaluation of Health Care Strategies
Knowledge Exchange & Dissemination
The National Network
ARCC
Seminars
Health Services Research Seminars
THETA Rounds
St. Michael's
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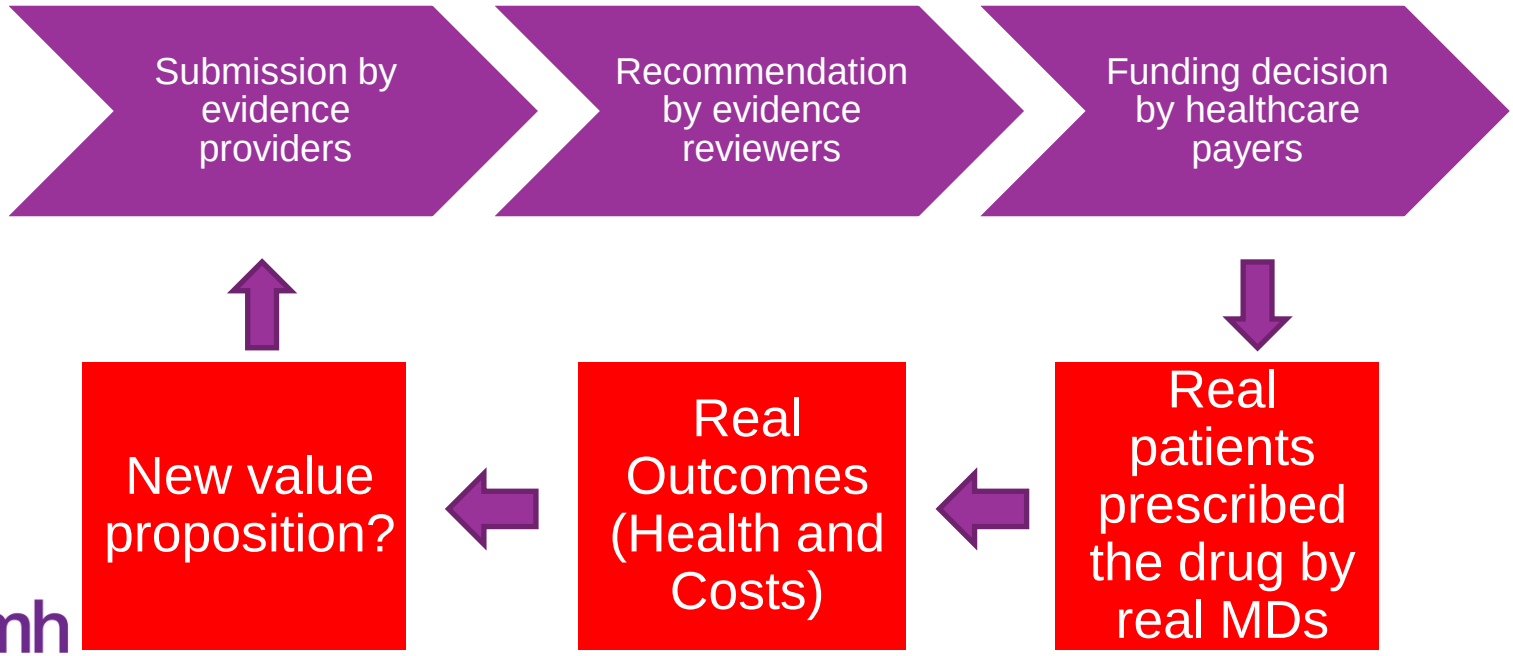
Maybe research can help



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Results - I

5 year

ALL

ΔC = $16,300

ΔE = 0.26

ICER = 62,000

ludes > 15 researchers, makers and clinicians.

lking the new drug were rom those who didn't e adjusted for selection

<60

ΔC = $9,000

ΔE = 0.29

ICER = 32,000

Results differed by age and by time horizon

Khor et al. BMC Cancer 2014, 14:586
http://www.biomedcentral.com/1471-2407/14/586

BMC Cancer

RESEARCH ARTICLE Open Access

Real world costs and cost-effectiveness of Rituximab for diffuse large B-cell lymphoma patients: a population-based analysis

Sara Khor[1,2,3,4], Jaclyn Beca[1,2,3], Murray Krahn[3,5,6,7,11], David Hodgson[3,7,8,11], Linda Lee[9], Michael Crump[10], Karen E Bremner[6], Jin Luo[11], Muhammad Mamdani[2,7,11], Chaim M Bell[7,12], Carol Sawka[3,7], Scott Gavura[13], Terrence Sullivan[3,7,14], Maureen Trudeau[15], Stuart Peacock[3,16,17] and Jeffrey S Hoch[1,2,3,7,11*]

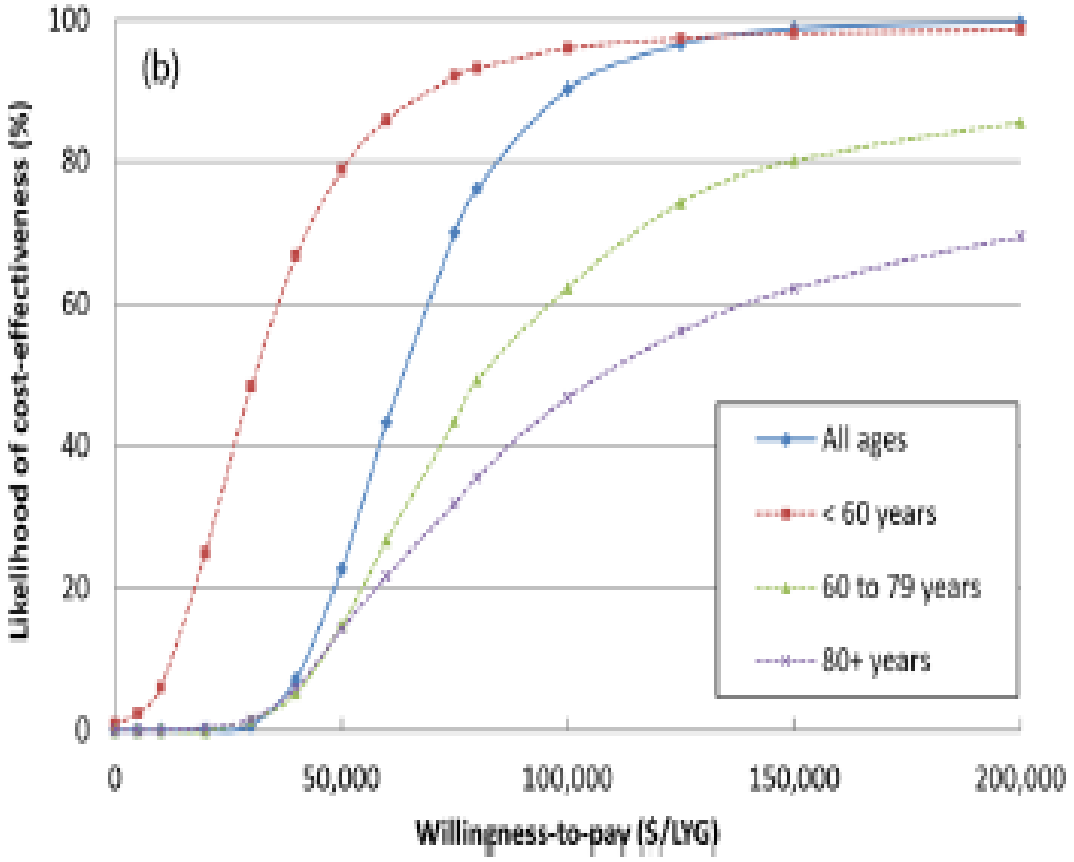
Abstract

Table 3 Mean cost by year and patient age at diagnosis

Mean cost (CAD$)	Year from diagnosis				
	1	2	3	4	5
All Ages					
CHOP	45089	10890	5415	4052	3549
RCHOP	63266	7733	5816	4343	4135
<60 yrs old					
CHOP	44401	12249	5211	3633	2787
RCHOP	60007	7031	5084	2825	2507
60-79 yrs old					
CHOP	46488	9678	6161	4926	4752
RCHOP	67364	8532	6254	4894	3774
≥80 yrs old					
CHOP	41490	6902	1988	1699	2034
RCHOP	64310	8465	7681	8142	5533

Results - II

The drug appears more cost-effective for younger patients



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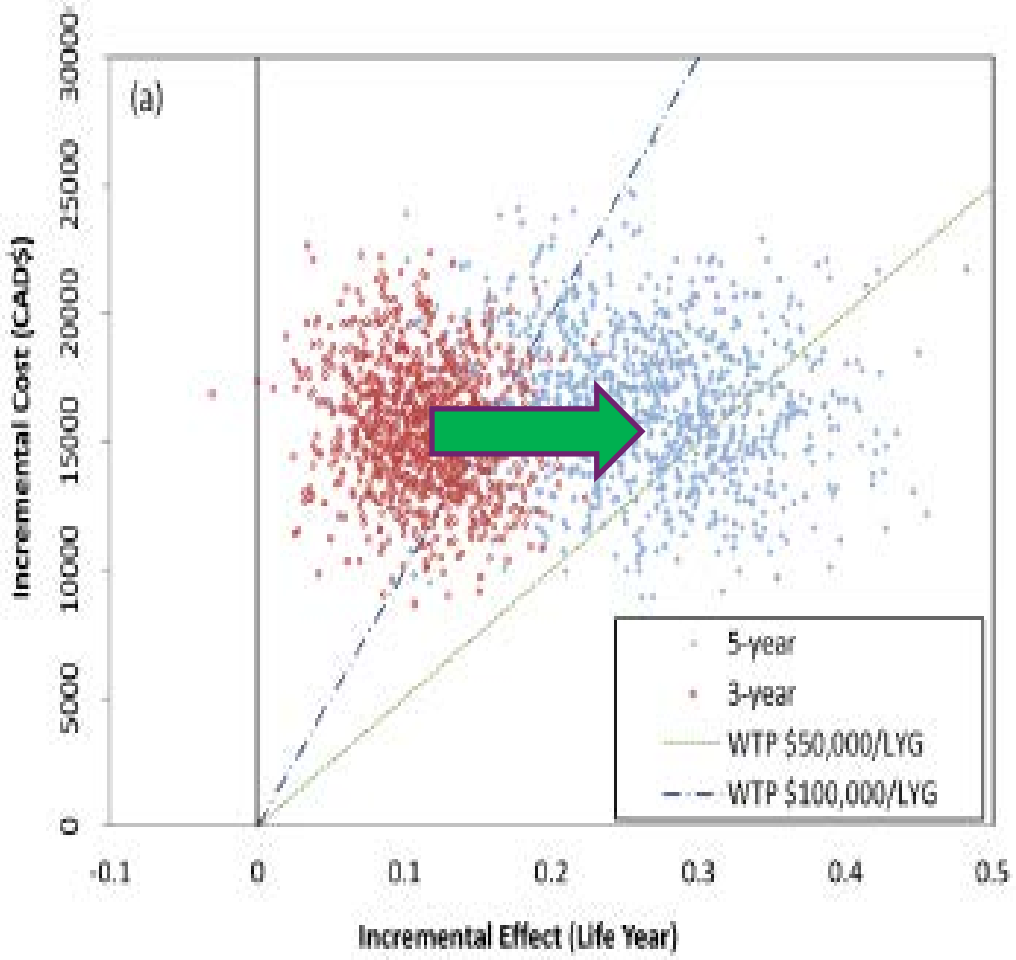
Results - III

The drug appears more cost-effective through time.



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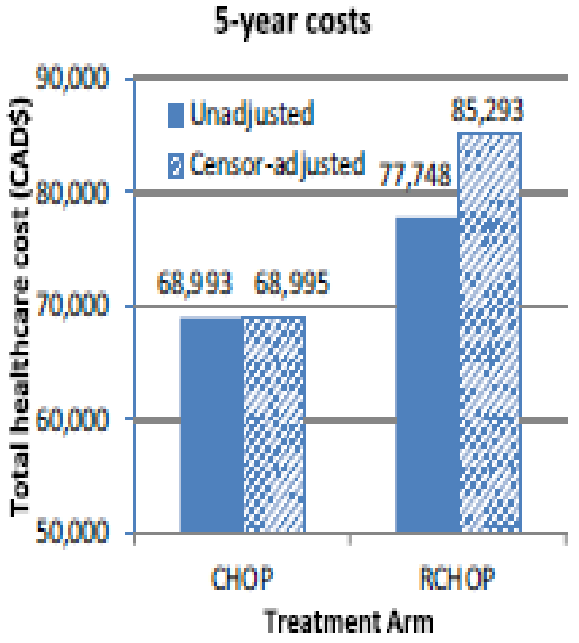
Technical lessons we learned

- Time mattered
  - trial-based (3 vs. 5) vs. modeling (vs. 10?)
- Methods mattered
  - “nonrandom selection”
  - Censoring
- Outcome matters
  - There and matters (mortality alway
  - long enough and short enough to s

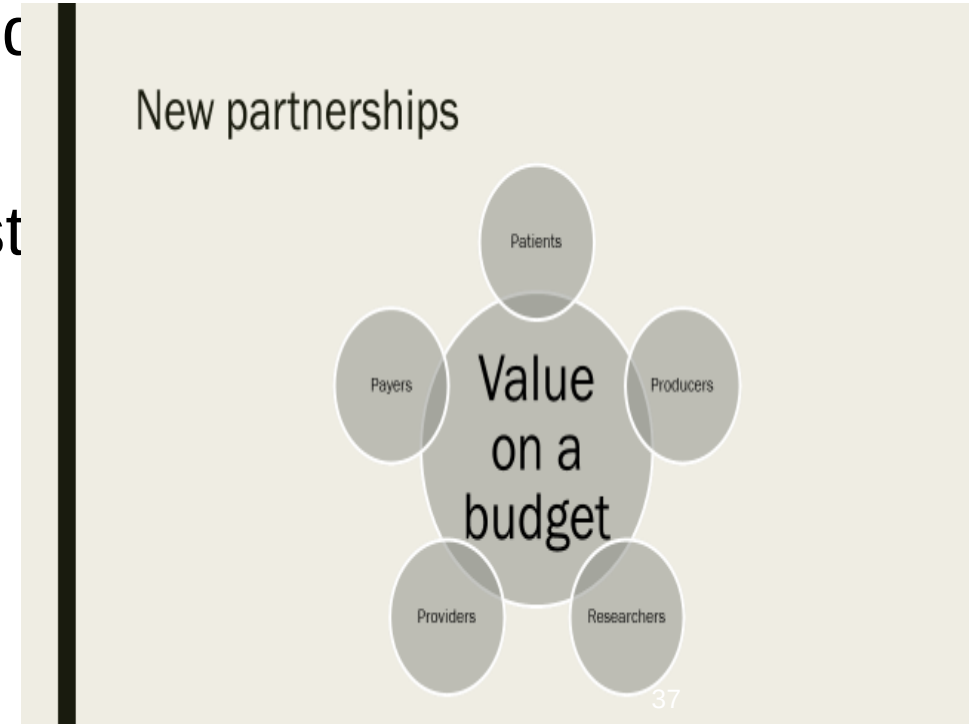


Future steps

- In a way that makes *all* parties feel comfortable, we must continue trying this by investing time, money and good will into examples we can build upon.

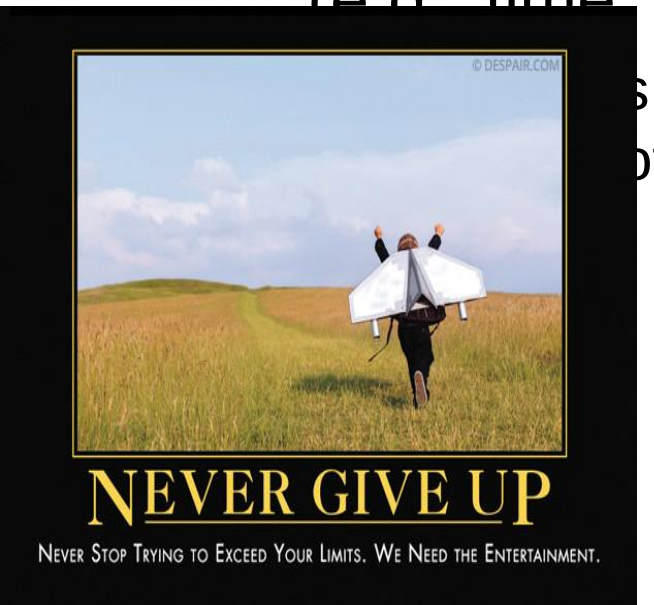
- Our study was one of the first examples, and others have continued

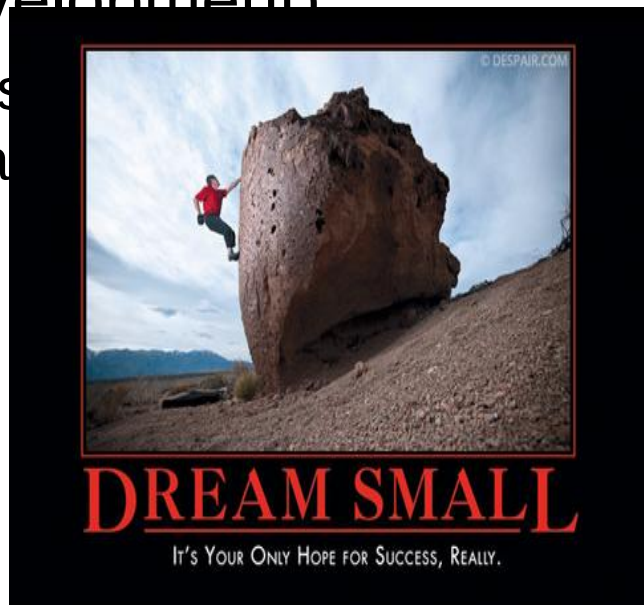
- In the future, we must challenges:
  - More partners
  - More products
  - More utility



Main points

- The “key” technical issues will change as the demand for RWE develops.
  - There will always be new things to figure out
- Things will not be 100% perfict, but we must build together.
  - This will be one piece of the solution
- Continued investment in the area is crucial (e.g., time, money, capacity development)
  - s will take resources inves
  - f cost-effectiveness data





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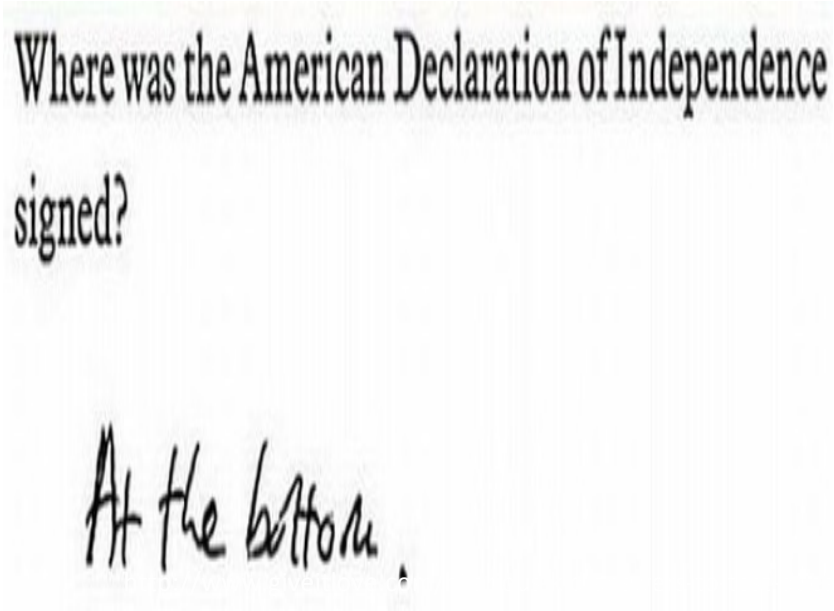

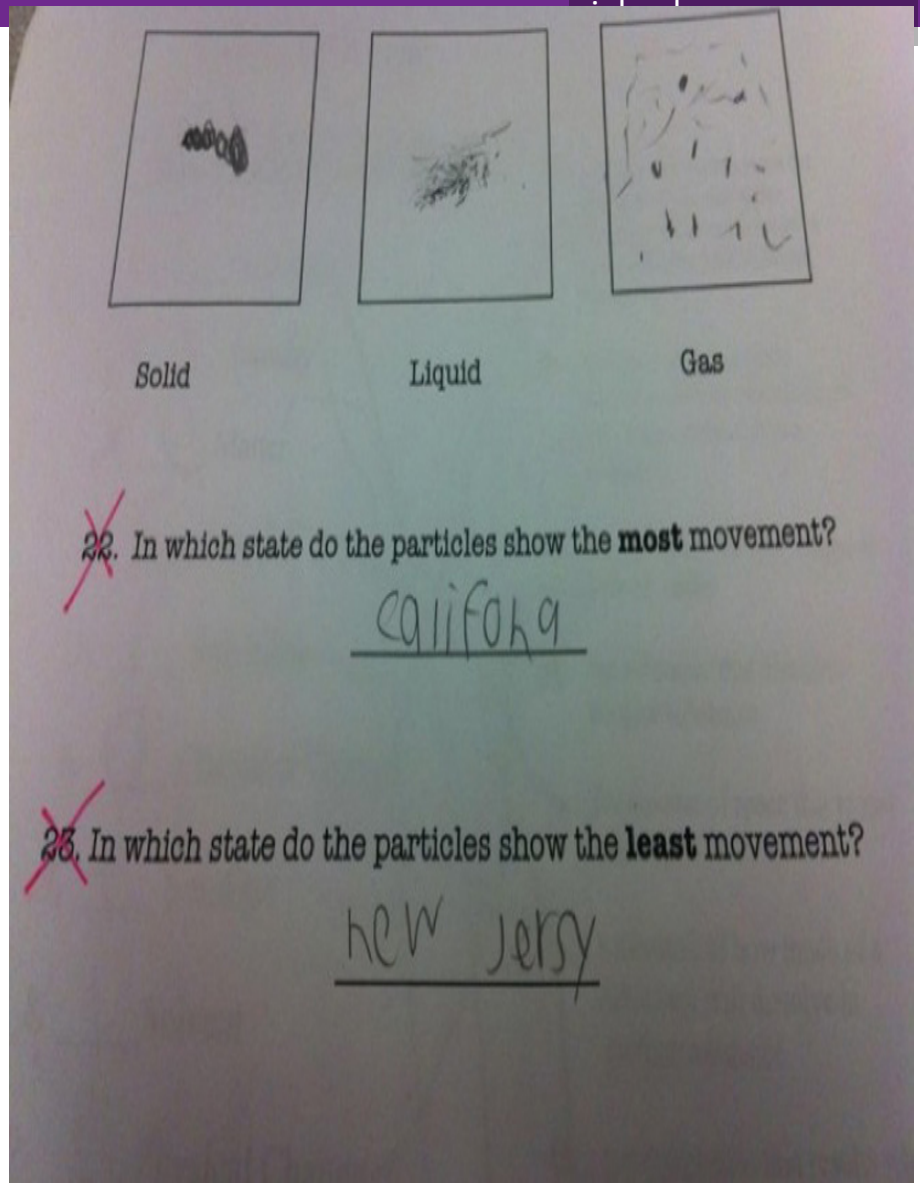

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- Medical Oncologist, Sunnybrook Odette Cancer Centre
- Associate Professor, University of Toronto
- Associate Scientist, Sunnybrook Research Institute
- Adjunct Scientist, ICES
- Co-Director, ARCC
- Chair, OSCCD
- Clinical Lead, Provincial Drug Reimbursement Programs, CCO

RWE: ARE WE READY TO DO IT?

Technical challenges and opportunities with example in RWE evaluation

CAPT Conference
Date: October 23, 2018

Dr. Kelvin Chan, Sunnybrook Odette Cancer Centre

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

The life cycle reassessment of Azacitidine

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Acknowledgements

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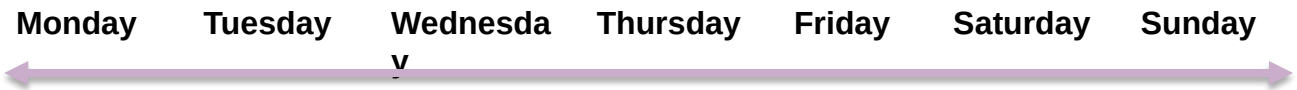
- Asmaa Maloul, CCO
- Liying Zhang, Sunnybrook Health Sciences Centre
- Jessica Arias, CCO
- Scott Gavura, CCO
- Kelvin Chan, CCO

Azacitidine: Background

- Treatment for Myelodysplastic syndromes (MDS) acute myeloid leukemia (AML)
- Funded in June 2010



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Azacitidine: Background

- Many cancer centres unable to administer chemotherapy on weekends
- Allowed administration based on 3 dosing schedules:

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Azacitidine: Objective

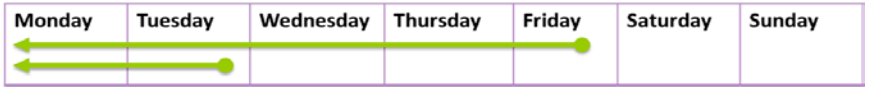
To validate different dosing schedules

- Are there differences between different dosing schedules?

7 Consecutive days

6 Consecutive days

5 + 2 Consecutive days



Azacitidine: Methods

Data provided from CCO (June 1, 2010 to March 2, 2016):

- **Additional data collected prospectively:**
  - Disease/patient characteristics prior to AZA initiation
  - Disease response
  - List of all treatments and doses received

Outcomes:

- Primary outcome
  - Overall survival (OS)
- Secondary outcomes
  - Disease response as per supplemental forms every 6 months

Analyses

- Survival curves by Kaplan-Meier method
- Univariate and multivariable Cox proportional hazard model

Azacitidine: Results

Characteristic	CCO population data (n = 1101)	AZA-001 (n = 179)
Age, years (range)	74 (19 to 99)	69 (42 to 83)
Male, No. (%)	718 (65)	132 (75)
IPSS classification (calculated)		
INT-2 risk, No. (%)	552 (64)	76 (43)
High risk, No. (%)	306 (36)	82 (46)
AML, No. (%)	276 (25)	55 (31)
Previous chemo, No. (%)	168 (15)	---
Intended dosing schedule		
7 consecutive days, No. (%)	272 (25)	179 (100)
6 consecutive days, No. (%)	137 (12)	---
5-2-2, No. (%)	692 (63)	---

Azacitidine: Results

Median number of cycles (IQR)	6 (3 to 11)	9 (4 to 15)
Median number of cycles for those receiving at least 4 cycles (IQR)	8 (6 to 14)	---
Best response		
Complete response, No. (%)*	49 (17)	30 (17)
Partial response, No. (%)*	31 (11)	21 (12)
Hematologic improvement, No. (%)**	166 (20)	87 (49)***
Overall survival, months	11.6****	24.5

*Of those with marrow done (n = 293)
**Of those with supplemental form (n = 814) and no CR/PR/PD on marrow
***Included those with CR/PR
****If therapy-related MDS excluded: 12.4 months (95% CI, 11.4 to 13.7)

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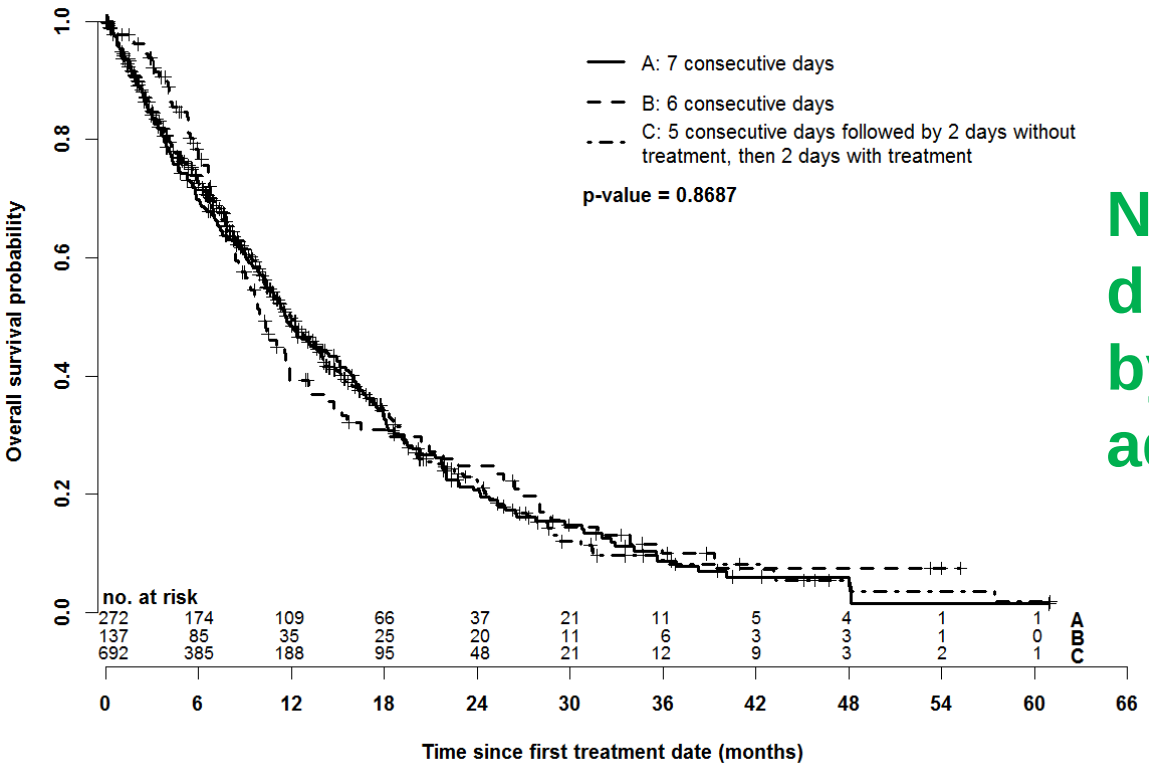
Azacitidine: Results



No significant difference in survival by drug administration type

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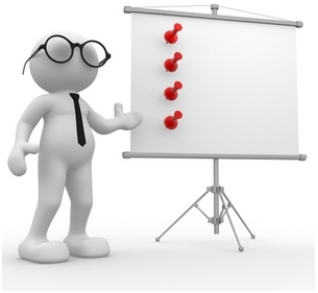
Azacitidine: Conclusion



Study findings presented to OSCCD

Ontario Steering Committee for Cancer Drugs (OSCCD)

The Ontario Steering Committee for Cancer Drugs (OSCCD) was created in 2013 to enhance and support the administration of Ontario's cancer drug programs. The committee advises the Ministry of Health and Long-Term Care's Ontario Public Drug Programs and Cancer Care Ontario's Provincial Drug Reimbursement Programs.

Committee Objective

The objective is to provide evidence-based clinical, health research and health economic guidance to the Executive Officer (EO) of Ontario Public Drug Programs (OPDP) on: provincial cancer drug funding policies and decisions, program evaluation and drug-specific studies, and enhancements to cancer drug programs or initiatives in Ontario. For more information on cancer drug funding and decision making in Ontario, please see the **Public Drug Funding and Administration** page or visit one of these sites:

- **Ontario Drug Benefit: How drugs are approved**
- **Drug Submissions: Status for Single-Source Submissions**

regimen)

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Lessons Learned

- ✓Planned evaluation at the time of drug funding
- ✓Coordinated evaluation at the provincial level
- ✓Made policy impact (lead to reassessment of drug funding)

Lessons Learned

Policy & Plan → Data → Methods → Reassessment

Outcome	AZA-001[1]	CCO	GFM[2]	GESMD[3]	PHAROS[4]
Number of patients	179	1101	282	251	121
Median number of cycles	9	6	6	6	8.5
Best response					
CR, No. (%)*	30 (17)	49 (17)	38 (14)	N/A	8 (12)
PR, No. (%)*	21 (12)	31 (11)	9 (3)	N/A	2 (3)
Heme improvement, No. (%)	87 (49)**	166 (20)	43 (15)	N/A	26 (39)**
Overall survival, months	24.5	11.6	13.5	13.4	16.9

Substantial difference **Considerable difference**

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Lessons Learned

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Lessons Learned

Policy & Plan | Data | Methods | Reassessment

✓ **Prospectively collect "NOT ROUTINELY COLLECTED" data**

Characteristic	CCO population data (n = 1101)	AZA-001 (n = 179)
Age, years (range)	74 (19 to 99)	69 (42 to 83)
Male, No. (%)	718 (65)	132 (75)
IPSS classification (calculated)		
INT-2 risk, No. (%)	552 (64)	76 (43)
High risk, No. (%)	306 (36)	82 (46)
AML, No. (%)	276 (25)	55 (31)

Outcome	CCO population data (n = 1101)	AZA-001 (n = 179)
Median number of cycles (IQR)	6 (3 to 11)	9 (4 to 15)
Median number of cycles for those receiving at least 4 cycles (IQR)	8 (6 to 14)	---
Best response		
Complete response, No. (%)*	49 (17)	30 (17)
Partial response, No. (%)*	31 (11)	21 (12)
Hematologic improvement, No. (%)**	166 (20)	87 (49)***

Base line confounder characteristic
- IPSS classification

Outcome variable
- Response rate

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Lessons Learned

Policy & Plan | Data | Methods | Reassessment

- ✓ **Planned to compare 3 regimens OS**
- ✓ **Population-based analyses**

Outcome	AZA-001[1]	CCO	
Number of patients	179	1101	

Represents **“entire patients”** receiving the drug

- No sample selection

- How many events we nee
- How long to collect data
- When to start data analys

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Lessons Learned

Policy & Plan | Data | Methods | Reassessment

- Not enough events to show significant findings
- Additional data collection can be viewed as data mining

- Patent expiring → Not useful for price negotiation
- Missing opportunity for early intervention if safety is concern

Lessons Learned

- ✓ **HTA (OSCCD) available to review, reassess and make a recommendation**

Where are we now?

Ontario
Cancer Care Ontario

Evidence Building Program (EBP)

The Evidence-Building Program (EBP) complements and strengthens Ontario's New Drug Funding Program (NDFP) and the process for making drug funding decisions in Ontario by maintaining rigour and consistency. The EBP seeks to resolve uncertainty around clinical and cost-effectiveness data related to the expansion of cancer drug coverage within Ontario.

For a cancer drug to be included in Ontario's EBP there must be evolving, but incomplete evidence of benefits. This will allow us to fund the drug on a time-limited basis to collect real-world data on its clinical and cost effectiveness. This data will be used by the Ministry of Health and Long-Term Care to help inform a final change to existing funding criteria.

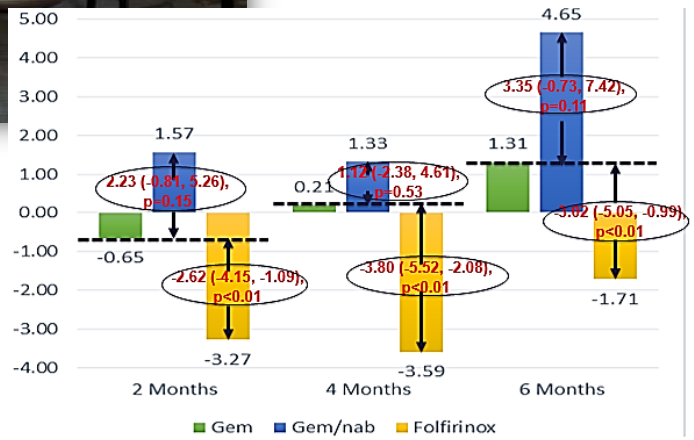
Where are we now?

Your Symptoms Matter Resources

Your Symptoms Matter is the new name for the symptom screening kiosk and tools. It is a set of questionnaires that let patients tell their health care team about their symptoms and how they are feeling. Patient responses are shared and reviewed with their health care team to help make decisions on how to best manage their symptoms. The new name will be rolled out at all centres in early October 2016.

A real-world population-based comparative symptom analysis of patients with advanced pancreatic cancer (APC) receiving first line FOLFIRINOX (FFX), gemcitabine + nab-paclitaxel (GnP) or gemcitabine (G)

Kelvin K. W. Chan[1,2,3], Lucy Qiao[1], Lisa Barbera[2], Helen Guo[1], Jaclyn Marie Beca[4], Ruby Redmond-Misner[4], Wanrudee Isaranuwatchai[4], Craig Earle[1,2,5], Scott R. Berry[2], James Joseph Biagi[6], Stephen Welch[7], Brandon M. Meyers[8], Nicole Mittmann[1,9], Natalie Coburn[2], Aliya Pardhan[1], Jessica Arias[1], Deborah Schwartz[1], Scott Gavura[1], Leta Forbes[1], Robin McLeod[1], Erin Diane Kennedy[1,10]



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Where are we now?

CanREValue

Value-based decisions from Real World Evidence

The **Can**adian **R**eal-world **E**vidence for **Value** of Cancer Drugs Collaboration

Brings together key stakeholders involved in Canadian cancer drug funding decision processes.

Developing a framework for the generation and use of RWE in cancer drug funding decisions