Establishing an evidence framework for evaluating treatment effectiveness in rare diseases

Kylie Tingley[1], Beth Potter[1], Doug Coyle[1], Lindsey Sikora[2], in collaboration with the Canadian Inherited Metabolic Diseases Research Network (CIMDRN)
1 School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, ON; 2 Health Sciences Library, University of Ottawa, Ottawa, ON

Rationale

- Comparative effectiveness research (CER) offers an approach to research with the explicit purpose of *"assisting consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population level"* (Sox & Greenfield 2009).
- Three key elements in CER approach (Sox & Goodman 2012; Sox & Greenfield 2009)
  1) Direct comparisons of available interventions
  2) Pragmatic perspective
  3) Informed choice for all stakeholders
- Primary methods for evidence generation in CER: randomized controlled trials (RCT), observational research, systematic reviews, and decision analysis (Sox & Goodman 2012)
- **Applying CER in rare disease context is challenging mainly due to small, clinically heterogeneous, and geographically dispersed patient population**
- For the purposes of comparing treatment effectiveness, few (or even zero) RCTs exist for any one treatment
- Most of the evidence in rare disease research falls in the lower levels of the traditional evidence hierarchy for evaluating interventions (Ho et al. 2008)

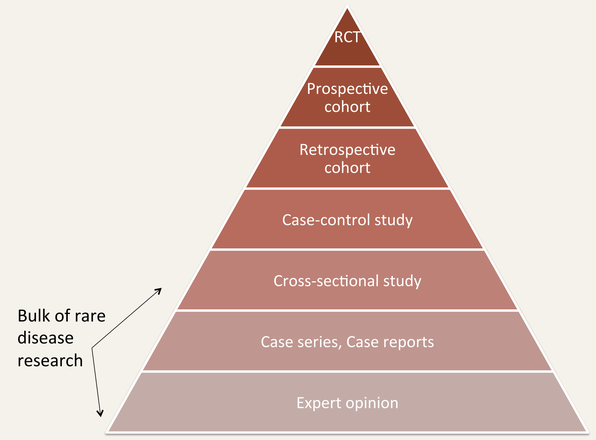

Figure 1. The traditional evidence hierarchy (adapted from Ho et al. 2008). The bulk of rare disease research accumulates in the lower half of the pyramid.

- Lower quality evidence is not recognized as part of traditional evidence synthesis methods, particularly in the context of policy decision-making

Objective

- To understand the value of considering evidence from alternative study designs in evaluating treatments for rare diseases (e.g., case series, quasi-experimental designs) – while recognizing the main risks of bias for each

References:

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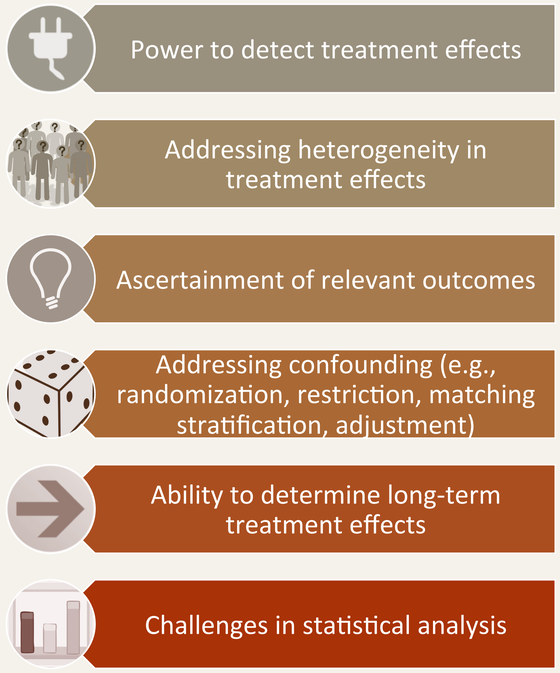
For more information please e-mail: Kylie Tingley, kting022@uottawa.ca

Methods

- Iterative, systematic and non-systematic searching to identify seminal papers in the following areas: evidence hierarchies for evaluating treatment effectiveness; risk of bias assessment for observational studies; methods and frameworks for evaluating treatments for rare diseases
- Critical review of the selected literature, including a qualitative synthesis to identify challenges specific to the rare disease context; ability of specific study designs to address these challenges; and risk of bias
- Literature will be summarized in the form of a framework to provide guidance for approaches to systematically reviewing treatment effectiveness evidence for rare diseases

Initial Findings

- From our initial literature review and consultation with members of the research team, we have identified six main challenges in generating evidence of treatment effectiveness for rare diseases:



- Example study designs found in the evidence base for evaluating treatment effectiveness in rare and their ability to address the six methodological challenges mentioned above. (Table adapted from Potter et al. 2015)

Explanatory RCT	+/-	-	+/-	+	-	+/-
Pragmatic RCT	+/-	+	+	+	+/-	+/-
N-of-1 trials	+/-	+	+	+/-	-	+/-
Cohort study	+	+	+	-	+	+/-
Case series	-	+	+	-	+/-	-

\+ addressing this aspect is a strength of this design
+/- addressing this aspect is variable
\- addressing this aspect is a weakness of this design

Next Steps

- We will summarize the identified literature in the form of a framework to provide guidance for approaches to systematically reviewing treatment effectiveness evidence for rare diseases
- Given that many studies rely on surrogate endpoints rather than clinically meaningful or patient-centred outcomes, this framework will also specifically consider the value and the risk of bias associated with using surrogate endpoints; and provide guidance about assembling the evidence required to establish their appropriateness
- We will also be conducting a case study using our framework to synthesize the evidence base that compares effectiveness of treatments for mucopolysaccharidosis type I (MPS I)

Case Study: MPS I

- Prevalence: approximately 1:100,000 live births (Moore et al. 2008)
- Spectrum of severity:
  - Mildly affected: diagnosed in adulthood; normal lifespan
  - Moderately affected: diagnosed during later childhood; death in 2nd or 3rd decade of life, if untreated
  - Severely affected: diagnosed < age 2; death < age 10, if untreated; severe cognitive impairment unique to this form of MPS I
- Currently available treatment options:
  - Moderately and some mildly affected patients typically treated with enzyme replacement therapy (ERT) using laronidase (D'Aco et al. 2012)
  - Severely affected receive early hematopoietic stem cell therapy (HSCT) as standard of care (D'Aco et a. 2012)
- Evidence suggests combination of ERT and HSCT might be beneficial for severely affected, no direct comparisons

Authors	Study Design	Number of patients	Age range (months)	Length of follow-up (months)	Treatments	Outcomes
Grewal et al. (2005)	Case series (multicenter)	12	8-18	1-7	ERT before and after HSCT	- survival - engraftment rate - transplant & non-transplant outcomes
Cox-Brinkman et al. (2006)	Case series (multicenter)	22	2-39	3-18	- ERT before and after HSCT - HSCT alone (historic controls)	- survival - engraftment rate - HSCT associated morbidity
Tolar et al. (2008)	Case series (single center)	7	7.8-22.5	6-28.5	ERT before and after HSCT	- engraftment rate - pulmonary complications
Wynn et al. (2009)	Case series (single center)	18	7-24	≥6	ERT before and after HSCT	- survival - engraftment rate
Eisengart et al. (2013)	Quasi-experimental (single center)	19	17.5 (7.9)[1]	24	- ERT before and after HSCT - HSCT alone	- neurocognitive development - engraftment rate - length of stay in hospital

[1]mean (standard deviation)

- ERT is very expensive, so how can existing evidence best be used to make informed clinical and policy-decisions?

Value

- It is expected that this work will provide insights into approaches for generating and synthesizing evidence about treatment effectiveness in the context of rare diseases and CER
- Information from this project will help policy-makers and clinicians, researchers, patients, and families to make informed medical decisions

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