New directions for trials to reduce cognitive & functional decline

A Population Health Research Institute Workshop

Hamilton, Ontario, Canada April 1-2, 2019

Cognitive and functional decline with ageing are major challenges for patients, families and health systems worldwide. To test the many plausible agents and treatment strategies at reasonable cost to academia and industry, clinical trialists must develop more efficient trials that also give reliable results.

The Population Research Institute (PHRI) has pioneered the science, design, and delivery of **efficient large-scale randomized trials** in cardiovascular disease. These trials have led to widespread adoption of treatments that have reduced the incidence of stroke, heart attack and other diseases. We believe that the application of efficient, large-scale trial design **to target cognitive and functional decline** will provide the ability to confidently answer important questions, reduce costs, and lead to generalizable therapies.

The key challenges for clinical trialists seeking to reduce cognitive and functional decline are that:

1. **Multiple pathologies may lead to cognitive impairment in most individuals:** protein folding disorders (e.g. tau, amyloid, alpha synucleins); vascular pathologies (i.e. small and large cerebrovascular diseases); and inflammation are all associated with cognitive and functional decline and are found together in many - perhaps the majority - of patients dying with dementia.
   If agents work on only one pathology, this implies the clinical trialist must either recruit very large numbers of individuals to a trial with clinical outcomes (although such sample sizes may be very large); or must measure the effect of an agents on biomarkers that are known to be causally related to cognitive and functional impairment. The most widely used biomarkers of pathologies of cognitive impairment are difficult to deliver at scale and are expensive (e.g. markers of cerebral small vessel disease, measurement of amyloid or tau by PET or CSF), and their association with clinical outcomes, particularly at older ages, is not clearly causal.
2. **Clinical outcomes are important:** for disabling diseases, preventing or delaying disability provides a more convincing test of efficacy than improving cognitive tests, imaging or other biomarkers. Although biomarker outcomes may be useful to choose between agents, large scale trials with impairment or activity limitation outcomes will be needed to demonstrate efficacy to convince patients, doctors, regulators and payers that treatments are worthwhile.
   A major challenge for the clinical trialist is that current science suggests a long latency between the potential for intervention and the occurrence of dementia, and how to deliver trial with such long follow up has not been resolved,
3. **The complexity and cost of proposed treatment strategies:** for a treatment to be adopted widely for a common disease, it has to simple. If, for example, PET targeted intravenous amyloid reduction strategies prove to be effective to reduce the rate of Alzheimer's disease this strategy could not be adopted widely unless costs for both PET scanning for screening large populations and treatment fall.

We will address the following questions during the workshop,

1. What is the rational, systematic approach to identifying and assessing candidate interventions?
2. What interventions are currently available to test?
3. Which populations are suitable to be recruited at scale?
4. What can be stripped from a complex trial to reduce costs?
5. Are biomarkers of targeted therapy needed during trial or as part of trial eligibility?
6. What cognitive outcomes should be measured?

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Attendees:

External participants:

Dr. Michelle Canavan	University of Galway, Ireland
Dr. Dan Case	Bayer Canada
Dr. Howard Chertkow	University of Toronto/Scientific Director CCNA/Rotman Research In.
Dr. Shurjeel Choudri	Bayer Canada
Dr. Tali Cukierman-Yaffe	Tel Aviv University, Israel
Prof. Martin O'Donnell	University of Galway, Ireland
Prof. Eric E. Smith	University of Calgary, Canada (remotely)
Prof. Sudha Seshadri	University of Texas, San Antonio and Framingham Study USA,
Dr. William Whiteley	Universities of Edinburgh & Oxford, U.K. (co-Chair)
Prof. Jeff Williamson	J Paul Sticht Center on Aging, Wake Forest School of Medicine, USA
Prof. Malcolm Macleod	CAMARADES collaboration, University of Edinburgh, U.K. (remotely)

McMaster / PHRI participants:

Prof. Sonia Anand	PHRI, Pop'n Health, co-PI Canadian Alliance of Healthy Hearts & Minds
Prof. Shrikant Bangdiwala	PHRI/Health Research Methods, Evidence & Impact, McMaster
Dr. Vinai Bhagirath	PHRI/Division of Hematology and Thromboembolism, McMaster
Prof. Jackie Bosch	PHRI/School of Rehabilitation Science, McMaster (co-Chair)
Prof. Hertzel Gerstein	PHRI/Director, Endocrinology & Metabolism, McMaster
Prof. Robert Hart	PHRI/Division of Neurology, McMaster (co-Chair)
Ms. Nidhi Jethoo	PHRI Senior Systems Administrator ICT
Dr. Shun Fu Lee	PHRI Statistics
Ms. Andrea Mead	PHRI/Meeting organizer
Dr. Mike Noseworthy	Department of Engineering, McMaster
Prof. Guillaime Pare	PHRI/Pathology and Molecular Medicine, McMaster
Dr. Marie Pigeyre	PHRI/Pathology and Molecular Medicine, McMaster
Prof. Parminder Raina	PHRI Epidemiology/Clinical Epidemiology & Biostatistics, McMaster
Ms. Karleen Schulze	PHRI Statistics
Prof. Mike Sharma	PHRI Stroke & Cognition/ Division of Neurology, McMaster
Ms. Ellison Themeles	PHRI Program Manager
Ms. Jessica Tyrwhitt	PHRI Program Manager
Prof. Salim Yusuf	PHRI/Division of Health Sciences, McMaster

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Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Monday 1st April

Location: Main Auditorium, Main floor, PHRI, David Braley Cardiac Vascular and Stroke Research Institute

		Title	People	Purpose
8:30		Coffee		
		1: INTRODUCTION		**Chair Hart**
9:00	15'	Introduction and welcome	Yusuf, Hart	Meeting aim: to define interventions outcomes prevention of cognitive & f
9:15	15'	PHRI experience in trials of cognition	Bosch	Results of PHRI trials so far. Reasons delivery of cognitive outcomes inte Delivery of imaging biomarkers at sca
9:30	15'	Discussion	Chair	Is this approach practicable for demen not taken off in dementia studies? possible at scale? What are the challen
9:45	30'	Blood pressure as an intervention for the prevention of cognitive decline: a successful intervention?	Williamson	Populations at risk: intensity, duration MIND
10:15	30'	Discussion	Chair	Why was the effect of BP lowering delivering trial at scale; why do one ra high risk populations; is this the last a brain imaging findings; lessons from c
10:45	15'	Tea break		
		2: INTERVENTIONS		**Chair Bosch**
11:00	15'	What has been tested already: systematic review of existing interventions	Whiteley	To summarize briefly agents that hav or within the next 6 months
11:15	15'	Discussion	Chair	Have these interventions truly failed; duration/ intensity the problem? Are
11:30	30'	Review of plausible interventions		Diet (Mente/Deghan), exercise (Bos sleep (O'Donnell), lipid modification (Whiteley)
12:00	30'	Discussion of plausible interventions	Chair	Are individual interventions plausible tested? What is currently most promis
12:30	45'	Lunch		Foyer
		3: POPULATIONS & OUTCOMES		**Chair Whiteley**
13:15	30'	What do population studies tell us about rates of decline in populations at risk: when and in whom to intervene	Seshadri	Which populations have high preva highest risk of cognitive decline and e
13:45	30'	Discussion	Chair	

14:15	20’	Characteristics of good outcome measures for cognition and function: practical implications	O’Donnell	
14:35	25’	Discussion	Chair	What are the cheapest and most effect most statistically efficient method of a
15:00	20’	Tea break		
		4. BIOMARKERS OF RISK, TREATMENT & DISEASE		**Chair Bosch**
15:20	30’	Biomarkers of disease: role in participant recruitment, target engagement and disease progression.	Seshadri	Biomarkers and their role in trials. Pot
15:50	30’	Discussion		Which outcomes are ready to be used there a role for simpler markers? Wha do the new FDA guideline mean for n
16:20	20’	Opportunities for biomarker research in PHRI	Pare	Polygenic scores to identify participan
16:40	20’	Roundup	Chair	
17:00		CLOSE		
18:30		Dinner		The Diplomat - 43 King William Stree

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Tuesday 2nd April

Location: Main Auditorium, Main floor, PHRI, David Braley Cardiac Vascular and Stroke Research Institute

		Title	People	Purpose
9:00		Coffee		
09:15	5'	Welcome back, summary, lessons learnt	Hart, Yusuf	
		5: STATISTICS		**Chair Whiteley**
9:20	30'	Why have trials been neutral: statistical commentary	Bangdiwala	
9:50	30'	Discussion	Chair	Are there improvements to be made i
10:20	15'	What are rational approaches to choosing interventions	MacLeod (remote)	Examples from multiple sclerosis, m systematic reviews.
10:35	15'	Discussion	Chair	Are adaptive, multiple factorial desig scale feasible or desirable?
10:50	15'	Using cohorts to recruit patients, and the Canadian Alliance for Healthy Heart and Minds	Anand	
11:05	15'	Discussion		Could cohorts be used effectively for
11:05	55'	(i) Interventions that are ready (short-list) (ii) Populations that are ready (short list) (iiii) Biomarkers of outcome (short list) (iv) Outcomes: function or cognition (short list) (v) Target grants	Chair	
12:00	30'	Round up, next steps, responsibilities	Hart, Yusuf	