

BC SUPPORT Unit

Real-World Clinical Trials Methods Cluster:

Report on Stakeholder Consultations for Methods Cluster Development

April, 2018

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Executive Summary

The BC SUPPORT Unit (the Unit), a component of the Strategy for Patient Oriented Research (SPOR), is a multi-partner organization created to support, streamline and increase patient-oriented research throughout BC. The **Real-World Clinical Trials Methods Cluster** is one of six Unit Methods Clusters. In the summer through fall of 2017, the Methods Cluster undertook a variety of consultations with stakeholders including hosting a planning event to inform a multi-year work plan. This document reports on those activities.

A total of 40 stakeholders, including trial methodologists, healthcare providers, patients/public members, and a BC Ministry of Health representative, attended the planning event. Ideas generated from this meeting and stakeholder feedback from subsequent webinars, teleconferences and individual meetings with trial methodologists and researchers led to the identification and confirmation of three themes to be of primary importance for development by the Methods Cluster:

- Theme 1:** Enhancing generalizability and individualized treatment: ensuring treatment needs in the broad population are addressed but with a focus on individual patient priorities (PROMs) and needs (precision medicine).
- Theme 2:** Addressing real world limitations: making trials feasible and efficient in real world settings (constraints on blinding, randomization, sample size, operational procedures, ethical considerations).
- Theme 3:** Leveraging external information sources: making use of non-trial information (published literature, health databases/medical records, expert opinion) to get answers more quickly and enhance the value of a trial.

Within these three themes, a total of 10 ideas, most of which cross-cut multiple themes, were identified as potential projects. Based on the responses from an expression-of-interest survey, and taking into account respondents expressed level of involvement, five project ideas were applicable and feasible for further development. Project Leads self-identified in response to an open-call for leadership. These projects were:

1. Approaches to developing composite outcomes that reflect individual patient priorities. Co-Leads: Joel Singer & Nick Bansback
2. Developing causal analysis methods for comparing per-protocol effectiveness that accounts for individual patient priorities. Lead: Ehsan Karim
3. Increasing statistical efficiency including: (1) Evaluating and optimizing power in non-standard trial designs and (2) Improving the utilization of prior information. Lead: Hubert Wong
4. Improving recruitment and consenting processes. Lead: Penny Brasher
5. Develop methods for conducting registry-based trials. Co-Leads: Xibiao Ye & Penny Brasher

The RWCT MC is now working with teams to move these five projects forward.

1.0 Overview

The BC SUPPORT Unit (the Unit) is a multi-partner organization with a goal to support, streamline and increase patient-oriented research across British Columbia (BC). Launched in November 2016, the Unit has created six Methods Clusters to focus on advancing the science in areas contributing to patient-oriented research. The **Real-World Clinical Trials (RWCT) Methods Cluster** has a mandate to build capacity and foster methodological advancement in the field of clinical trials. To develop a work plan, the Methods Cluster hosted a planning event on September 11, 2017 in Vancouver. The meeting objectives were to:

1. Establish a foundation: What is patient-oriented research? What is the role of the methods clusters? What are methods? What is a real-world clinical trial?
2. Initiate discussion for a shared vision: Identify key components of a RWCT which would be appropriate for methods development. Explore the feasibility and potential resource requirements.
3. Stimulate the development of a community that will contribute to the cluster.

Prior to the planning event, Methods Cluster Lead Dr. Hubert Wong held informal consultations with clinical trial methodologists across the province. The individual conversations and a pre-meeting survey provided an understanding of participants' background, expertise, and expectations of the meeting. The meeting was attended by 40 stakeholders: trial methodologists, healthcare providers, patient/public partners, and a BC Ministry of Health representative. After the meeting, a second survey was distributed. Webinars were also held for people who were unable to attend the planning event so as to provide an opportunity to share the key information from the planning event and invite feedback.

Based on these consultations, the RWCT Methods Cluster identified themes and potential project ideas. These results were distributed to stakeholders and an open call for expression-of-interest was disseminated to identify the level of stakeholder support for each potential project idea. Ideas with sufficient stakeholder support (i.e. adequate numbers of individuals committed to (1) leadership and (2) collaboration) were identified to serve as the foundation for a work plan (Figure 1).

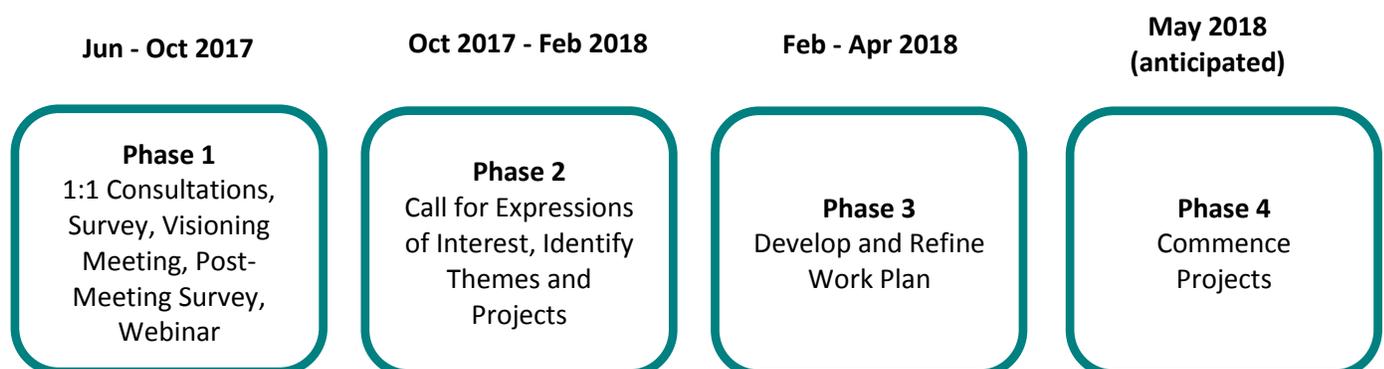


Figure 1: Process and Timeline

2.0 Real-World Clinical Trials Methods Cluster Planning Event

2.1 Establishing a Shared Foundation

Alison Hoens, KT Specialist for the Methods Clusters, opened the meeting by presenting an overview of the principles of patient-oriented research, the background to the CIHR SPOR initiative, and the role of the BC SUPPORT Unit and its Methods Clusters. Dr. Hubert Wong continued with an explanation of the features of real-world clinical trials and outlined the types of work that would fall within the scope of the RWCT Methods Cluster.

2.2 Pre-Event Survey Results

Dr. Wong presented results from the pre-meeting survey, which was completed by 31 individuals (Methodologists: 15; Trial support providers: 7; Trial investigators: 5; Other: 4). Current strengths for real-world clinical trials in BC identified by respondents included: 1) a large group of individuals with expertise spread across the province, 2) the strong collaborative culture and desire for multi-disciplinary collaboration, 3) the availability of data sources including population data and clinical information systems, and 4) support from organizational structures such as the public health care system, resources from the SUPPORT Unit and Ministry of Health backing. Major gaps identified included: 1) lack of consideration of individualized treatment, 2) lack of engagement and training of stakeholders, 3) the uncertainty around the generalizability of trial results to the real world, and 4) a lack of resources – infrastructure and expertise – to conduct RWCTs.

2.3 Bridging Perspectives

Robert Reinhard, a long-time patient advocate in HIV/AIDS, and a community-based researcher, presented a talk titled “Lessons Learned by a Patient Oriented Research Advocate to Promote Health Improvement Impacts and Suggest Future Directions in RWCT”. Key issues highlighted by Mr. Reinhard were: (1) when designing RWCTs, all stakeholders should be involved and should be trained to enable them to contribute appropriately, (2) non-traditional designs will be needed to make trials feasible in the real world, and (3) The only question that matters is: Are people’s health better off than they were before from implementing something that you studied?

2.4 Identifying Opportunities and Addressing Feasibility

Participants were allocated into small groups representing a diversity of perspective and asked to identify key components of RWCTs which would be appropriate for methods development by the cluster. Each group presented their ideas to all participants and the information was captured by graphic recording and voice recording for later transcription. The groups were then asked to explore the feasibility and potential required resources for addressing the ideas that had been generated.

3.0 Post-Event Survey

Seventeen people who attended the Planning Event responded to a post-event survey. The survey comprised three questions on a four-point Likert scale (response options; Strongly Agree, Agree, Disagree and Strongly Disagree) about the Planning Event's organization, content, and value as well as two open-ended questions relating to moving the RWCT Methods Cluster forward. In regard to organization, all respondents agreed or strongly agreed that the objectives of the Planning Event were clear, the event was well organized, and there was sufficient time scheduled for small group work and large group discussion. At least 15 of 17 respondents agreed or strongly agreed that their understanding of patient-oriented research, real-world clinical trials, and the BC SUPPORT Unit and Methods Clusters, was enhanced and that the presentation by Robert Reinhard was valuable. Similarly, 16 of 17 respondents agreed or strongly agreed that the Planning Event stimulated the development of a 'community' for RWCT methods development, and was a good start to discussion about potential areas of focus for RWCT methods development.

Responses to the open-ended questions in the post-event survey included positive feedback about the meeting and the RWCT Methods Cluster initiatives – specifically the evidence of committed and passionate participants and the opportunity for collaboration. There were a few concerns expressed regarding “how this will work” given challenges such as busy people finding the time to make these projects a priority and the logistics of how to effectively undertake them.

4.0 Post-Meeting Webinar

On October 10, 2017, a webinar that included key material from the Planning Event was held for stakeholders who were unable to attend. A total of seven individuals including patient partners, healthcare providers and industry attended in real-time and eight individuals have subsequently accessed the recording. Key messages were shared and input invited.

5.0 Identification of Cluster Projects

Based on the meeting recordings, minutes, and post-meeting consultations, the following three themes and potential project ideas were identified:

1. Enhancing generalizability and individualized treatment: ensuring treatment needs in the broad population are addressed but with a focus on individual patient priorities (PROMs) and needs (precision medicine). Potential projects include:

- Approaches to developing composite outcomes that reflect individual patient priorities (e.g. using discrete choice experiments and appropriate analytic models; combining individual level priorities with individual level trial outcomes to obtain individualized net benefit scores)
- Approaches to designing “mini-trials” that can be aggregated into a “big” trial
- Developing causal analysis methods for comparing per-protocol effectiveness that accounts for individual patient priorities
- Integrating precision medicine considerations in trial design and analysis

2. Addressing real world limitations: making trials feasible and efficient in real world settings (constraints on blinding, randomization, sample size, operational procedures, ethical considerations). Potential projects include:

- Developing hybrid effectiveness-implementation designs
- Evaluating and optimizing power in non-standard trial designs (e.g. step-wedge designs with varying cluster sizes; realized power distribution of a randomization scheme; adaptive trial designs)
- Improving recruitment and consenting processes (e.g. simplifying consent using technology; identifying patients’ subgroups with different preferences for consent procedures)

3. Leveraging external information sources: making use of non-trial information (published literature, health databases/medical records, expert opinion) to get answers more quickly and enhance the value of a trial. Potential projects include:

- Analytic methods for combining heterogeneous data sources to support decision-making (both patient and policy)
- Develop methods for conducting registry-based trials
- New approaches to eliciting joint prior distributions for treatment effects

Based on the responses from the expression-of-interest survey, and taking into account respondents expressed level of involvement, five project ideas were selected for further development under the guidance of Project Leads who had self-identified interest in leading each project. These projects were:

1. Approaches to developing composite outcomes that reflect individual patient priorities. Co-Leads: Joel Singer & Nick Bansback
2. Developing causal analysis methods for comparing per-protocol effectiveness that accounts for individual patient priorities. Lead: Ehsan Karim
3. Increasing statistical efficiency including: (1) Evaluating and optimizing power in non-standard trial designs and (2) Improving the utilization of prior information. Lead: Hubert Wong
4. Improving recruitment and consenting processes. Lead: Penny Brasher
5. Develop methods for conducting registry-based trials. Co-Leads: Xibiao Ye & Penny Brasher

6.0 Next Steps

The RWCT Methods Cluster Lead and the KT Specialist Alison Hoens are currently working with Project Leads and teams in developing proposals that will internally reviewed by the BC SUPPORT Unit Science Council and then subsequently be sent to external reviewers for comment. The final proposals will be incorporated into a work plan to guide the activity of the Cluster over the next 3 years.

Appendix A: Pre-Planning Event Survey Responses

Table A1: Summary of Identified Gaps in RWCTs in BC and Sample Comments

Gap	#of responses	Sample Comments
Lack of consideration of individualized treatment	5	“a therapy ... optimal for a population does not necessarily mean that it will be the choice for all individuals”; “need to include patient’s perspective and patient-reported outcomes”
Lack of engagement and training of stakeholders	5	“who are the stakeholders that we need to engage ...?”; “patient engagement in developing research questions”; “limited collaboration among RCT methodologists & end users”
Generalizability of trial results to the real world is uncertain	4	“trials often do not take into consideration standard of care practices of the area when designing inclusion/exclusion criteria”; “methodologies so strict that they apply to a very limited # of patients”
Lack of resources (infrastructure and expertise) to conduct RWCTs	3	“No research infrastructure beyond large teaching hospitals”; “No community research infrastructure to do community based research”

Table A2: Summary of Identified Strengths in RWCTs in BC and Sample Comments

Strength	#of responses	Sample Comments
Expertise	13	“Active research community ... at local and provincial level”; “KT expertise that could be brought into the front end of study design”; “Good RCT methodologists in BC”; “Underutilized expertise outside of academic centers”
Collaborations	8	“Collaborative culture”; “Strong network of clinical investigators”; “Desire for multi-disciplinary collaboration”
Data sources	7	“Good population data”; “Clinical information systems that are increasingly capable of answering questions MoH data cannot”
Support from organizational structures	3	“Public health-care system”; “Resources from the SUPPORT Unit”; “Patient engagement a MoH-backed initiative”

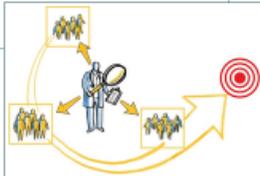
Table A3: Summary of Desired Outcomes from the Planning Event and Sample Comments

Desired outcome	#of responses	Sample Comments
Understanding of RWCTs	9	“Gain a better understanding of RWCT from others perspectives and develop/foster networks ... moving forward”; “To learn about the current status of RWCT in BC”
Collaboration opportunities	7	“To learn more about possible areas for collaboration ... how to best make lasting impact on patient care”; “... build provincial/ regional/local infrastructure/collaboration to support RWCTs”
Learning about RWCT methodology	5	“Learn some flavor about what the important problems are, what could be feasible, and whether or not I have the relevant expertise to contribute”; “Have a few ideas for outside-the-box methodological work”
Learning about his cluster’s vision	4	“... see the overall vision of the cluster and [get] a sense of the support and resources ...”; “Appreciation of local expertise and plans for future work”

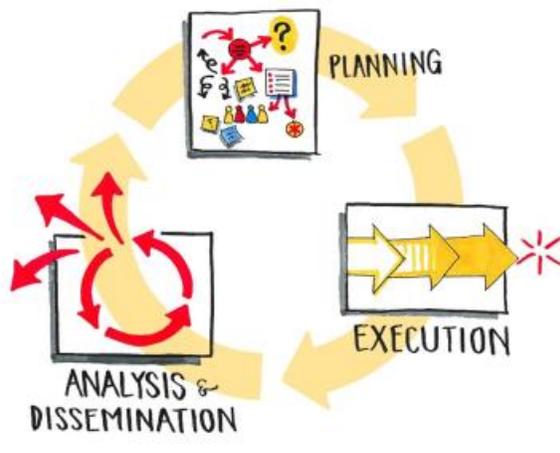
Appendix B: Definitions

Clinical Trial vs Real World Clinical Trial

<p>Clinical Trial</p> <p><i>A research study that prospectively assigns humans to one or more interventions to evaluate the effects on health outcomes. (WHO)</i></p> <p>Traditionally conducted in idealized settings to give an intervention its best chance to demonstrate a beneficial effect; often involving:</p> <ul style="list-style-type: none"> • Narrow patient population • Well-controlled settings; interventions delivered by “experts” • Close monitoring during study follow-up • Emphasizes one “primary” outcome (often clinical efficacy) 	<p>Real World Clinical Trial</p> <p>A trial intended to answer how well interventions work in the real world</p> <p>Seeks to:</p> <ul style="list-style-type: none"> ▪ Include broad patient population. ▪ Deliver interventions in usual care settings using minimal extra resources. ▪ Evaluate multiple outcomes that are important to patients. <ul style="list-style-type: none"> • In reality, “real world”-ness falls in a continuum, not a dichotomy!
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Clinical trial methodology



The procedures used to minimize bias, maximize efficiency, and enhance generalizability and value:

- **Planning:** defining population and intervention(s), selecting outcome measures, subgroup analysis, randomization, blinding, number of patients needed.
- **Execution:** recruitment, consenting patients, follow-up, data collection, outcome assessment, clinical & data monitoring.
- **Analysis and dissemination:** estimating impact & uncertainty, reporting, supporting patient & policy decision-making.

