Adaptive Platform Trial Scientific Meeting

September 28 – 29 • Toronto, Canada

CanTreatCOVID

Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings

Mastering grant writing and protocol development for APTs

Adaptive Platform Trials Scientific Meeting

September 29, 2023

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Disclosures

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Speakers Bureau/Honoraria: **None from for-profit/commercial entities.**

I have received honoraria for presentations at Queen's University (2010), University of Saskatchewan (2012), Mount Sinai Hospital (2012), Toronto Reference Library (2016), Law Society of Ontario (2016), Japan Network of Health Promoting Hospitals & Health Services (2018), Ghent University, Belgium (2020), Joint Centre for Bioethics, University of Toronto (2019, 2021), North American Primary Care Research Group (2021), Ryerson University (2021), DFCM, U of T (2022)

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Other: I serve as an unpaid scientific advisor to a start-up company, Mutuo Health Solutions.

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

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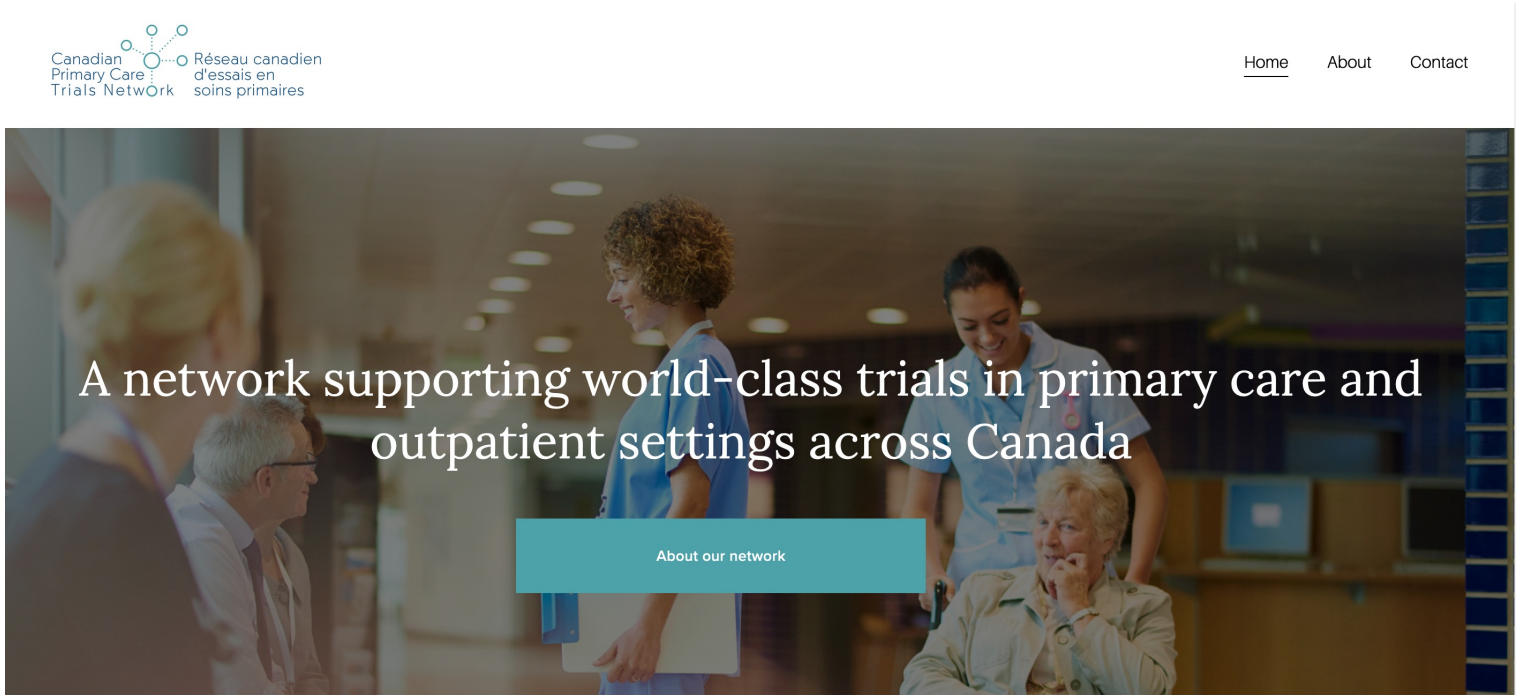
www.CanTreatCOVID.org

Canadian Primary Care Research Network
Réseau canadien de recherche en soins primaires

Canadian Primary Care Trials Network
Réseau canadien d'essais en soins primaires



https://primarycaretrials.ca/

Canadian Primary Care Trials Network | Réseau canadien d'essais en soins primaires

Our motivations

- Many RCTs are conducted with patients that **do not represent the broad diversity** of our patient populations*, and in **contexts that are far different** than general primary care
- Although the data is limited, **only a small % of CIHR** funding for trials are awarded to faculty in primary care.
- Most trials that come to primary care researchers are **led by people outside of primary care,** who seek us out to simply help with recruitment

*Orkin AM et al. JAMA Network Open 2021; 4(6)
https://pubmed.ncbi.nlm.nih.gov/34076703/

Canadian Primary Care Trials Network | Réseau canadien d'essais en soins primaires

Practice-Based Research Networks

- "Laboratories for discovery"
- Networks of organizations (e.g. primary care organizations, specialist practices, hospitals, local public health units)
- Working cooperatively to address pragmatic research questions.
- Bound by a shared commitment to improve health through systematic inquiry
- Central coordination: staff, REB applications, data sharing, analysis

Modified from Peterson K et al. AFM 2012; 10: 560-567

Objectives

- Review key components of a grant application for an adaptive platform trial (APT)
- Identify critical success factors and common challenges to building such a grant application
- Help attendees develop a rough outline for a grant application for an APT
- Discuss the key parts of a Master Protocol

Key items for any grant

- **Assemble a small team** to help with the grant application, including staff to keep track of admin items (e.g. signatures, CVs, participant table)
- As early as possible – have the grant team **read through the instructions** in detail – and then develop a Gantt chart (tasks and deadlines)
- Review **institutional requirements** (e.g. deadlines for institutional sign off, internal peer review, review of budget)
- Reach out early to **co-applicants, knowledge users, collaborators, and trainees** to identify your intent to apply and organize an initial planning discussion & touchbase meetings
- Aim to **assemble all the key parts** for ~1-2 weeks before the deadline, uploading items to the submission site
- If possible, engage **additional staff** with expertise in budgets, patient and community engagement, graphics

Big picture items to keep in mind for your APT grant

- Why is this condition really important? More important than numerous other conditions?
  - Scale of the problem: number impacted, lives lost, disability, cost
  - Urgent need (e.g. pandemic) or growing issue
  - Past treatments have failed or complete absence of data
  - Community and policymakers are strongly supportive
- Why is this urgently needed now, instead of 10 years from now?
- Why is an APT – by far – the best methodology to use?
- Why are you and your team the absolutely best people to conduct this work?

Making the argument for an APT

- Remember: many reviewers may not be familiar with APTs
- **Define APTs early in the grant** and point to existing examples and the impact
- Remember that APTs are particularly useful when studying:
  - Multiple possible treatments
  - New arms to be added as they emerge
  - Multiple centres all coordinated through a Master Protocol
  - Rapidly changing circumstances and evidence

How can your APT take advantage of routine clinical care, and be embedded in systems?

Use evidence to influence continual improvement

Collect data and analyze results to show what does and does not work

Disseminate

Share results to improve care for everyone

In a learning health care system, research influences practice and practice influences research

Internal and External Scan

Identify problems and potentially innovative solutions

Apply the plan in pilot and control settings

Design care and evaluation based on evidence generated here and elsewhere

Internal

External

Greene SM et al. Ann Int Med 2012; 157: 207-210

Key components of an APT grant: using CIHR standard headings

https://cihr-irsc.gc.ca/e/39187.html

1. The need for a trial, and specifically an APT

Brief summary of the entire proposal

1.1 What is the problem to be addressed?

Focus on a condition or situation, with a set of possible treatments or interventions

1.2 What is the objective(s) and the principal research question(s) to be addressed?

1.3 Why is a trial needed now? E.g. Provide evidence from the literature. Furthermore, give references to any relevant systematic review. If you believe that no relevant previous trials have been done, give details of your search strategy for existing trials.

1.4 How will the results of this trial be used? (E.g. contribute to knowledge translation, such as improving understanding, informing decision making and treatment guidelines, etc.) *Who is on your team to ensure KT happens?*

Ideal if direct link to guidelines or practice or policy

1.5 Are there any risks to the safety of participants involved in the trial? Please describe.

1. The need for a trial, and specifically an APT

"Three major problems are faced by clinicians, provincial decision makers and public health leaders::

- All published studies have been in unvaccinated patients. **It is unclear whether and to what extent existing therapeutics are effective in partially or fully vaccinated patients.**
- **Therapeutics have not been compared to one another**, and the comparative effectiveness, safety and cost-effectiveness/cost-utility has not been established.
- **Currently, no therapeutic has been evaluated specifically for its potential in reducing the likelihood of post-acute sequelae of SARS-CoV-2 ("long COVID")."**

Table 1: Oral therapeutics for SARS-CoV-2 in community settings as of May 17, 2022

	Cost per patient	**Key studies**	**NNT per hospitalization prevented (assume 5% risk of hospitalization)**[13]
fluvoxamine	~$10.85[14]	Stop COVID 1 Stop COVID 2 TOGETHER	80 (48-667)
budesonide	~$68.70[14]	STOIC CONTAIN Covis Pharma PRINCIPLE	72 (45-400)
nirmatrelvir/ritonavir	~$673.49§	EPIC-HR EPIC-SR†	12 (11-15)
molnupiravir‡	~$891.31§	Hetero Pharma MOVe-Out MOVe-Out Ph 2	50 (18-59)

§Cost of nirmatrelvir/ritonavir or molnupiravir paid by the Gov't of Canada cannot be divulged, per the contracts signed. Our estimates are based on the amounts publicly reported that entities in the United States paid, converted to Canadian dollars.[15]

† Full trial results not yet available.

‡ Not yet approved by Health Canada

1. The need for a trial: Evaluation criteria

- Present and future **resource implications** for healthcare and the economy in general.
- Are the **hypotheses** to be tested and/or the study objectives specified and described clearly?
- Is the trial **addressing the right question(s)**?
- Is this the **right time** to conduct the trial with respect to current knowledge of the intervention and current use of existing technologies?
- Are the **reasons for the study** and the changes that might be implemented as a result of the study adequately explained?
- What **evidence** is available to inform the need for and design of this trial (e.g.: systematic reviews)?
- Is the proposed research **compatible with the extent of the available knowledge**, nationally and internationally?
- What **impact** will the results have on practice or our understanding of the proposed intervention or underlying condition?
- Will the **results of the trial be generalizable** beyond the immediate research setting of the trial in a way that will maximize the impact of the results?

https://cihr-irsc.gc.ca/e/39187.html

2. The proposed trial

P: Population

I: Intervention

C: Control

O: Outcome(s)

T: Timeline

Population:	Patient population deemed at moderate to high risk of progression to severe disease by current Canadian data, currently: older adults (50+) years old or 18-49 with 1+ chronic medical condition or who are immunosuppressed with positive SARS-CoV-2 test (PCR or RAT), within 5 days of symptom onset
Intervention:	nirmatrelvir 300 mg/ritonavir 100 mg BID x 5 days
Control:	usual care
Outcome (primary):	hospitalization or death at 28 days
Outcome (second.):	time to recovery; symptom severity; incidence of post-acute sequelae of SARS-CoV-2; quality of life; costs and cost/QALY

2. The proposed trial

2.1 What is the proposed trial design? E.g. Open-label, double or single blinded, individual or cluster RCT, stepped wedge design

PICOT in a box, separate from text

2.2 What are the planned trial interventions? Both experimental and control.

Even though many Rx may eventually be tested, would be important to provide 1-2 treatments.

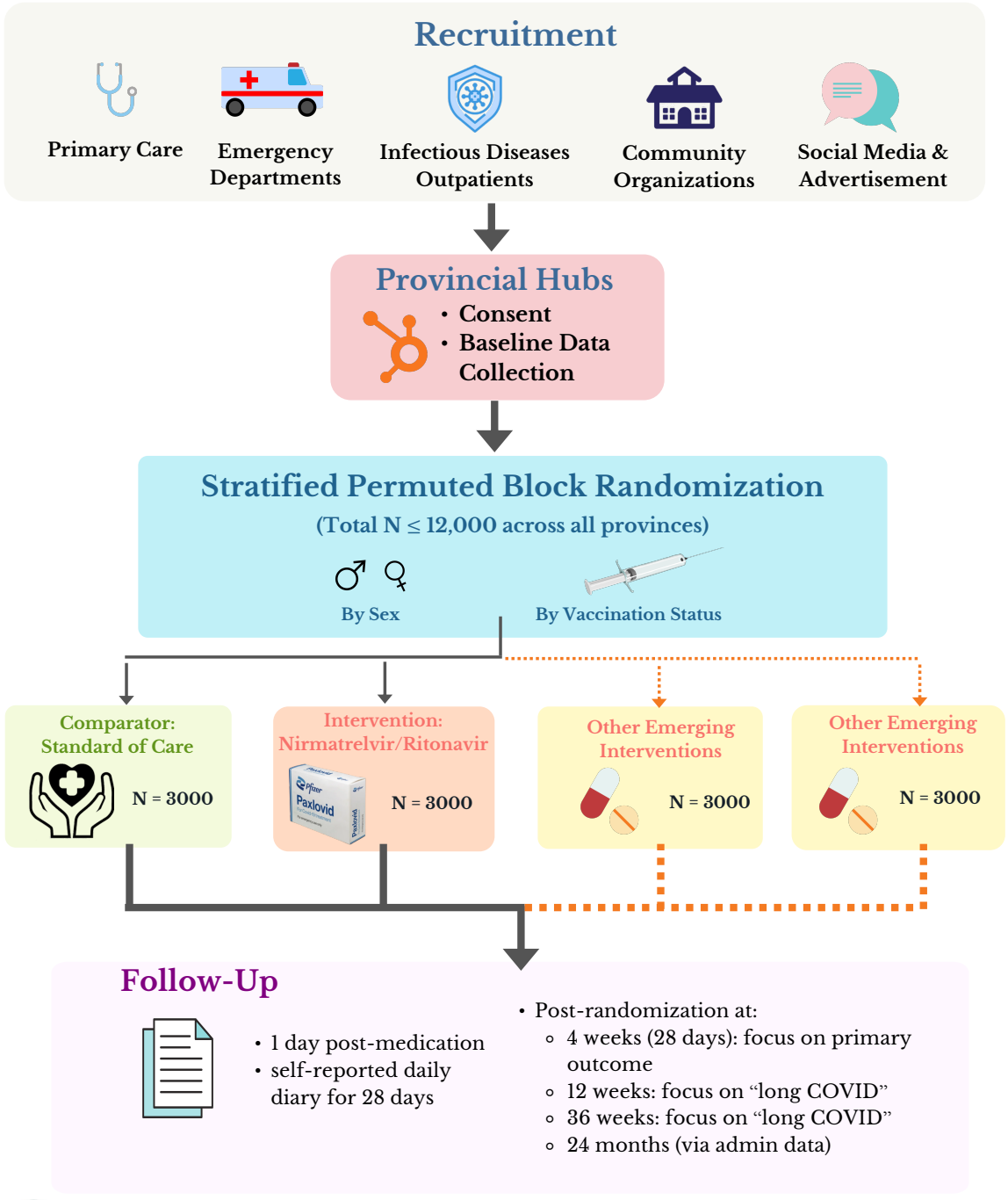
2.3 What are the proposed practical arrangements for allocating participants to trial groups? E.g. Randomization method. If stratification or minimization are to be used, give reasons and factors to be included.

Consider a figure, with multiple arms

2.4 What are the proposed methods for protecting against sources of bias? E.g. Blinding or masking. If blinding is not possible please explain why and give details of alternative methods proposed, or implications for interpretation of the trial's results.

2.5 What are the planned inclusion/exclusion criteria?

Can-ADAPT COVID Study



Protecting against bias

"In this open-label adaptive platform trial, the participant and recruiting clinicians will know which treatment is being used, but **the trial team will be blinded** to the interim and final analyses. …

Others including the Steering Committee will not have access to randomization allocation or data that may break blind (such as intervention duration) during the trial. The **pragmatic nature of this adaptive platform trial increases external validity**.

However, we will collect information about **contamination** (being prescribed study medications outside the trial) and co-interventions such as taking inhaled steroids. We will mitigate against **attrition bias** by ensuring that participants are compensated for answering outcome questions regardless of adherence to the study protocol. "

2. The proposed trial

2.6 What is the proposed duration of treatment period?

2.7 What is the proposed frequency and duration of follow up?

2.8 What are the proposed primary and secondary outcome measures?

Why? Why are these important, and have they been identified by patients, policymakers or providers?

2.9 How will the outcome measures be measured at follow up?

Is it feasible?

2. The proposed trial

2.10 What is the proposed sample size and what is the justification for the assumptions underlying the power calculations? Include both control and treatment groups, a brief description of the power calculations detailing the outcome measures on which these have been based, and give event rates, means and medians etc. as appropriate. (N.B. It is important to give the justification for the size of the difference that the trial is powered to detect. Does the sample size calculation take into account the anticipated rates of non-compliance and loss to follow-up given below?)

Consider a small table with varying power, size of effect.

Cite pilot work you have done, or existing studies.

Table 2: Power and sample size requirements using risk of hospitalization or death at 28 days

90% power			80% power		
Control	Treatment	N per arm	Control	Treatment	N per arm
5.0%	3.3%	**2981**	5.0%	3.3%	2256

"When this proposed trial is ready to start, it is likely our sample size assumptions and simulations will need to be updated. Prior to the closer start date … simulations will be performed to finalize and calibrate analysis rules that can control the nominal type I error rate at 5% and optimize statistical power and sample sizes. We have provided our sample size justification based on the best available evidence as of …. 202X."

2. The proposed trial

2.11 If applicable, are health service research issues be addressed? Justify inclusion/exclusion of health economics and quality of life measures. If these measures are to be included full details should be given including power calculations.

2.12 What is the planned recruitment rate? How will the recruitment be organized? Over what time period will recruitment take place? What evidence is there that the planned recruitment rate is achievable?

Role of PBRNs and past work. Can you demonstrate feasibility, e.g. pilot RCT?

2.13 Are there likely to be any problems with compliance? On what evidence are the compliance figures based?

2.14 What is the likely rate of loss to follow up? On what evidence is the loss to follow-up rate based?

Pilot data and consider inflating sample size to account for loss to follow-up

2.15 How many centers will be involved?

GOT COVID?

HAVE YOU TESTED IN THE PAST 5 DAYS USING A PCR OR HOME TEST?

ARE YOU:

50 years of age or older **OR** Between **18** - **49** years old with one or more **chronic conditions**

GOT ANY OF THESE SYMPTOMS?

- Fever or chills
- Cough
- Shortness of breath
- Decreased or loss of taste or smell
- Runny nose or nasal congestion
- Headache or fatigue
- Sore throat
- Muscle aches or joint pain
- Gastrointestinal symptoms

JOIN OUR CAN-ADAPT COVID STUDY!

EXAMPLE

You will be helping us learn which current and emerging **oral treatments for COVID-19** best help reduce the risk of severe illness and long-COVID.

To learn more or to sign up:

- Scan the QR code or visit: www.CanADAPTCOVID.ca **or**
- Call **1-800-CAN-COVD**

During the study, you will...

- Receive by chance an **approved oral treatment for COVID-19** or the current usual care.
- Have access to a **24-hour toll-free safety line.**
- Complete an **online diary** each day for 28 days and a **survey** at 12- and 36-weeks.

HAVE YOU TESTED POSITIVE FOR COVID?

Help us find therapies that reduce COVID symptoms & hospitalizations.

Who can participate?

- Canadian residents
- 50 years of age **OR** 18 - 49 years old with one or more chronic condition(s)
- who are within the first 5 days of experiencing COVID-19 symptoms

What will you do?

- Complete a daily diary for 14 days and fill out surveys
- Receive an honorarium of $30 per follow up

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

Health Canada | Santé Canada

Public Health Agency of Canada
Agence de la santé publique du Canada

Site preparation and readiness

- ❑Site Investigator identified: Requires each site to be aware of the interests, availability and experience of each potential SI
  - ❑Qualified Investigator Undertaking Form & Protocol Agreement signed
  - ❑CVs (signed) and licenses as required
- ❑REB identified & forms available: Requires knowledge of each REB process, incld. CTO
- ❑Staff and HR policies (where applicable)
  - ❑Training for TCPS2, GCP, Health Canada Division 5
- ❑Contracts (where applicable)
- ❑Medical directive/Delegated act process & establish delegation log
- ❑Finances (e.g. research cost centre)
- ❑Recruitment processes: posters, emails, staff, on-site, pre-authorization to be contacted
- ❑Process to communicate about the trial to the site
- ❑Data storage & consent documentation
- ❑Site Initiation Visit
- ❑Drug storage: standard operating procedures, temp. monitoring, logs
- ❑Insurance
- ❑Process to address any new identified health concerns, crisis management

2. The proposed trial

2.16 What is the proposed type of analyses?

2.17 What is the proposed frequency of analyses?

2.18 Are there any planned subgroup analyses?

Could include equity and sex/gender considerations

2.19 Has any pilot study been carried out using this design?

2. The proposed trial: Evaluation criteria

- Is the study **design appropriate** to answer the research questions posed?
- Has sufficient account been taken within the study design of the **issues of generalizability and representativeness**?
- What is the **justification** for the hypothesis underlying the power calculations?
- Are the **outcomes, and their measures, clearly described** and appropriate to the scientific hypothesis?
- Has the **trial population been defined adequately** in relation to the target population so that the results will have meaning?
- Have the **measures been validated** specifically for the target population(s)?
- Is the **control group appropriate**?
- How will **sources of bias** be avoided or taken account of?

https://cihr-irsc.gc.ca/e/39187.html

3. Trial Management

3.1 What are the arrangements for day to day management of the trial? E.g. Randomization, data handling, and who will be responsible for coordination.

3.2 What will be the role of each principal applicant and co-applicant proposed?

3.3 Describe the trial steering committee and if relevant the data safety and monitoring committee.

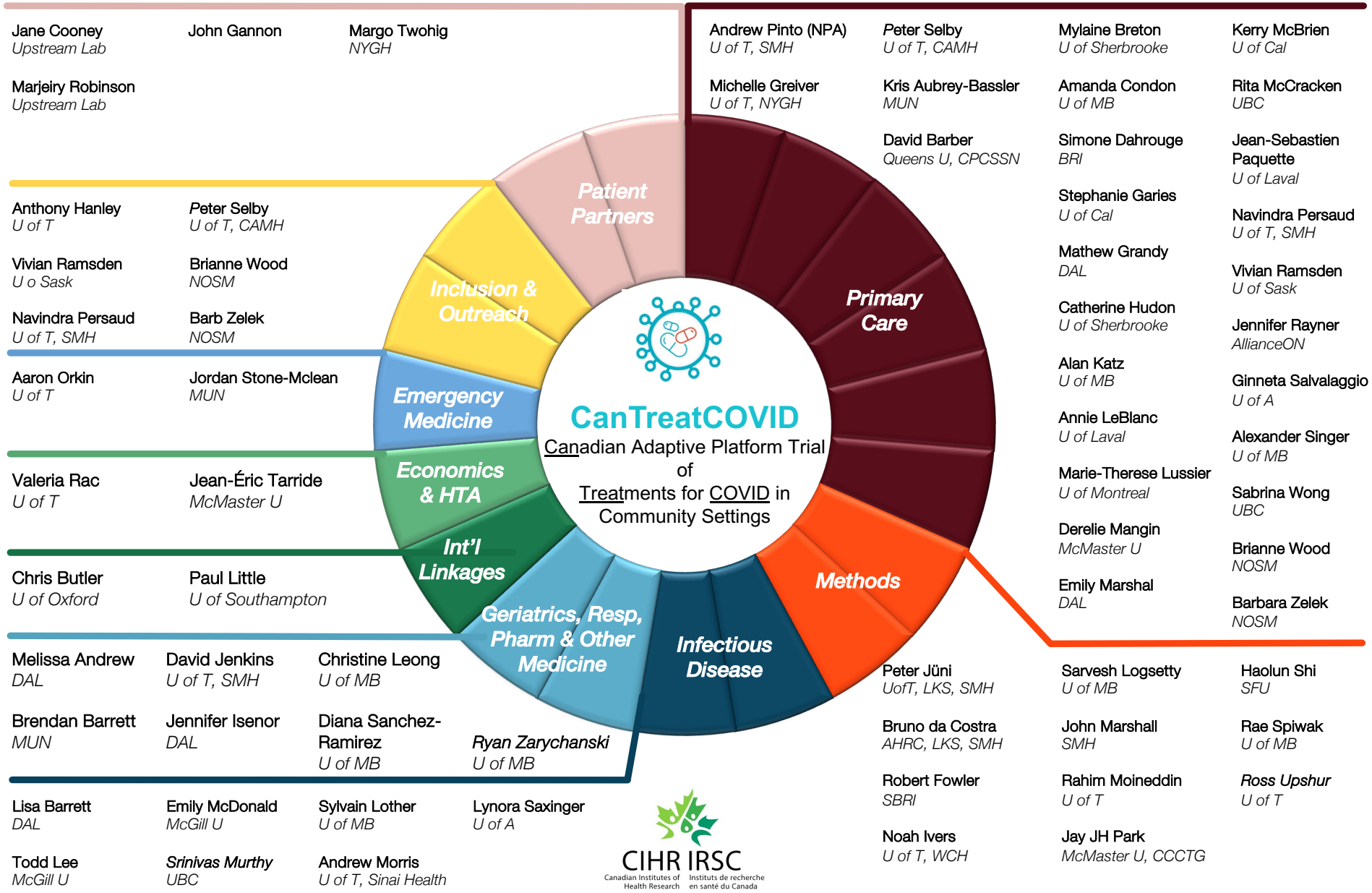
3. Trial Management

- Does the **proposed team of investigators have the necessary range of disciplines and experience** necessary to carry out the study?
- Does the trial team include **people with experience in successfully running large multi-center trials**?
- Has **adequate statistical advice** been sought and incorporated?
- Has adequate advice been sought and incorporated on **other health services research issues** if they are to be addressed?
- How will the **trial be coordinated**?
- What are the **roles** of members of the trial team?

3. Trial Management

Key committees:

- Steering Committee
- Statistical Analysis Committee
- Recruitment and Communications Committee
- Patient and Community Advisory Committee
- Therapeutics / Treatments / Interventions Committee
- Data Safety and Monitoring Committee



AllianceON = Alliance for Healthier Communities; **BRI** = Bruyère Research Institute; **CAMH** = Centre for Addiction and Mental Health; **CCCTG** = Canadian Critical Care Trials Group; **CPCSSN** = Canadian Primary Care Sentinel Surveillance Network; **DAL** = Dalhousie University; **MUN** = Memorial University; **NOSM** = Northern Ontario School of Medicine; **NYGH** = North York General Hospital; **SFU** = Simon Fraser University; **SBRI** = Sunnybrook Research Institute; **SMH** = St. Michael's Hospital; **LKS** = Li Ka Shing Knowledge Institute; **UBC** = University of British Columbia; **U of A** = University of Alberta; **U of Cal** = University of Calgary; **U of MB** = University of Manitoba; U of Sask = University of Saskatchewan; **U of T** = University of Toronto; **WCH** = Women's College Hospital

Key challenges

- Is this problem important and will it resonate with reviewers (who are not in primary care)?
- Recruitment!
- Building your team (quickly):
  - Site investigators as co-As (with letters of support)
  - Experienced team members… but also learners and ECRs to build capacity, and budgeting for grad students
  - Knowledge users, particularly policymakers, but also specialist colleagues in this area
  - Statistician
  - Health economist

Other tips

- **Clear and concise summary**: Background & Importance, Goals/aims, Methods, Expertise, Expected Outcomes
- **Sex & gender based analysis** throughout
- Consider **technical/prelim data** in Appendix
- Budget that is reasonable!
- **Gantt chart** as figure or Appendix
- Careful use of bold, underline and white space
- Read CIHR Peer Review Manual or equivalent

Questions?

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