Ontario Critical Care Clinical Practice Rounds (OC3PR): COVID-19

Feb 4 2021

Learning from our Practice:
How Clinical Studies Enrolling Critically Ill COVID-19 Patients from all ICUs Can Improve Care

Chaired by Dr. Dave Neilipovitz

Presented by Dr. John Marshall, Dr. Alexandra Binnie, and Dr Jennifer Tsang

Meeting Etiquette

- Participants will be muted and can use the chat function to converse with the panelists.
- Attendees can submit questions using the Q&A function on the Zoom menu. They can also "up vote" any questions their colleagues submit
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COVID-19:

The Power of Collaborative Research

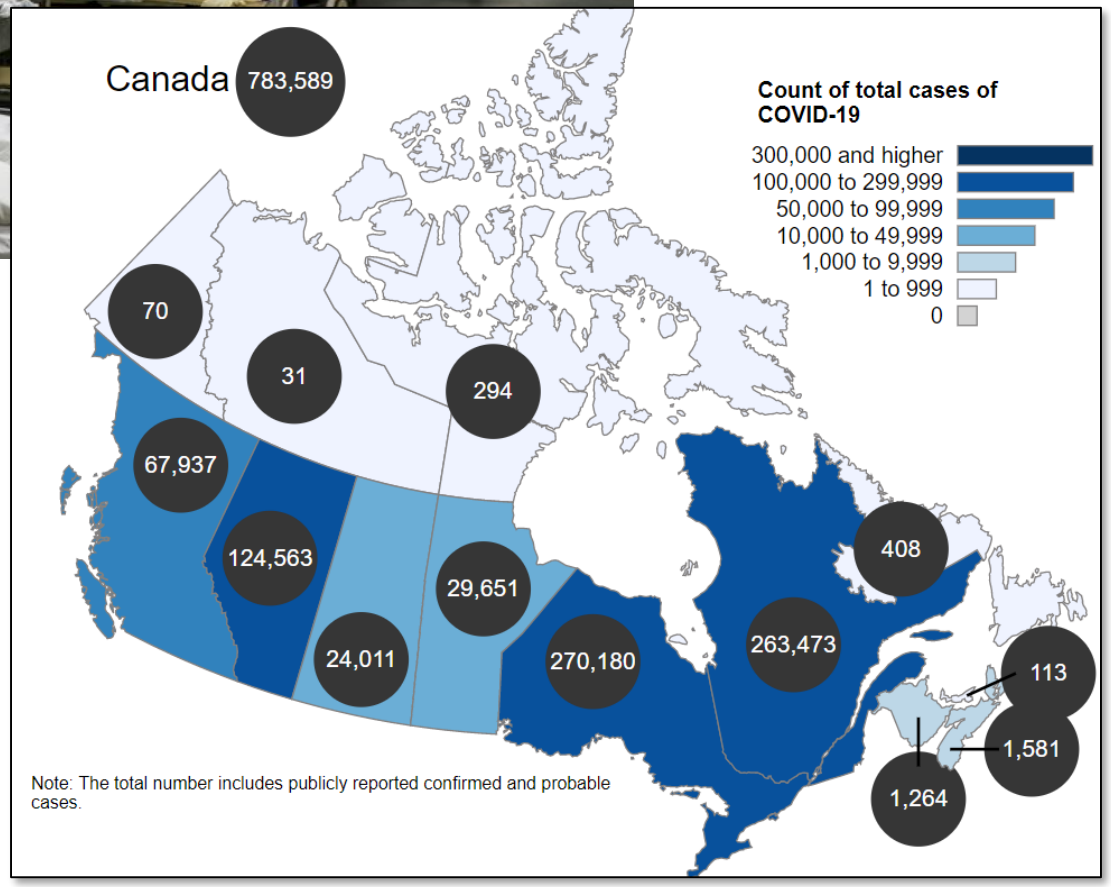
John C. Marshall MD FRCSC

OC3PR

February 4, 2021

St. Michael's Hospital

University of Toronto


Canada
783,589
Count of total cases of COVID-19
300,000 and higher
100,000 to 299,999
50,000 to 99,999
10,000 to 49,999
1,000 to 9,999
1 to 999
0
70
31
294
67,937
124,563
24,011
29,651
270,180
263,473
408
113
1,581
1,264
Note: The total number includes publicly reported confirmed and probable cases.

Search Details

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Showing: 1-10 of **4,636** studies 10 studies per page Show/Hide Columns

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting NEW	Dexamethasone for **COVID-19**	• **Covid19**	• Drug: Dexamethasone	• University of Oklahoma Medical Center Oklahoma City, Oklahoma, United States
2	☐	Recruiting	Duvelisib to Combat **COVID-19**	• **COVID-19**	• Drug: Duvelisib • Procedure: Peripheral blood draw • Drug: Placebo	• Washington University School of Medicine Saint Louis, Missouri, United States
3	☐	Enrolling by invitation	**COVID** SAFE: **COVID-19** Screening Assessment for Exposure	• **Covid19**	• Behavioral: Saliva-based testing	• Penn Medicine Philadelphia, Pennsylvania, United States
4	☐	Recruiting	Immune Modulators for Treating **COVID-19**	• **Covid19**	• Drug: Infliximab • Drug: Abatacept • Drug: Remdesivir • Drug: cenicriviroc	• University of Arkansas Medical Sciences Little Rock, Arkansas, United States • Scripps Clinical Medical Group La Jolla, California, United States

4636 Studies

- New clinical trial models
- New mechanisms of data sharing

RECOVERY

Randomised Evaluation of COVID-19 Therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

World Health Organization

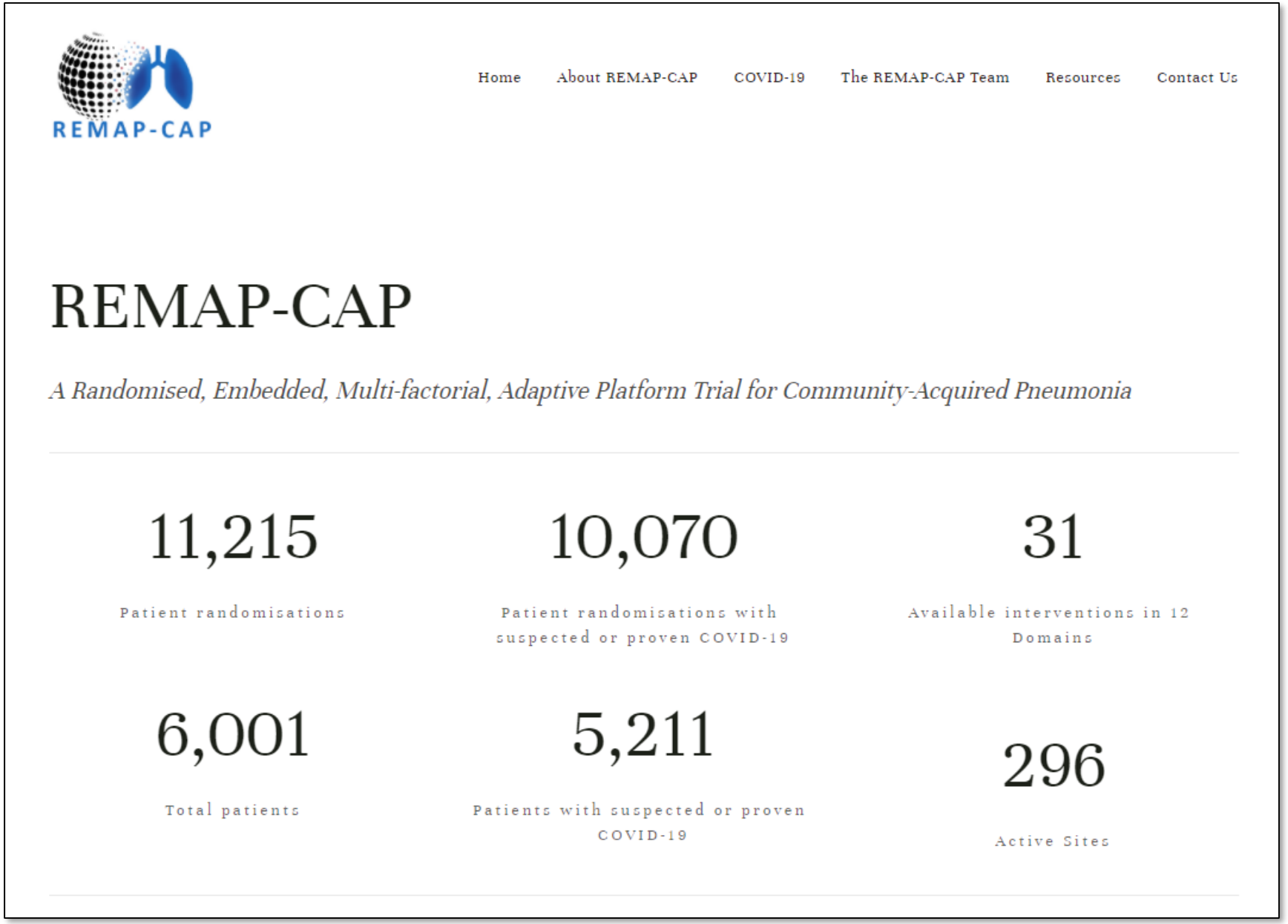
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

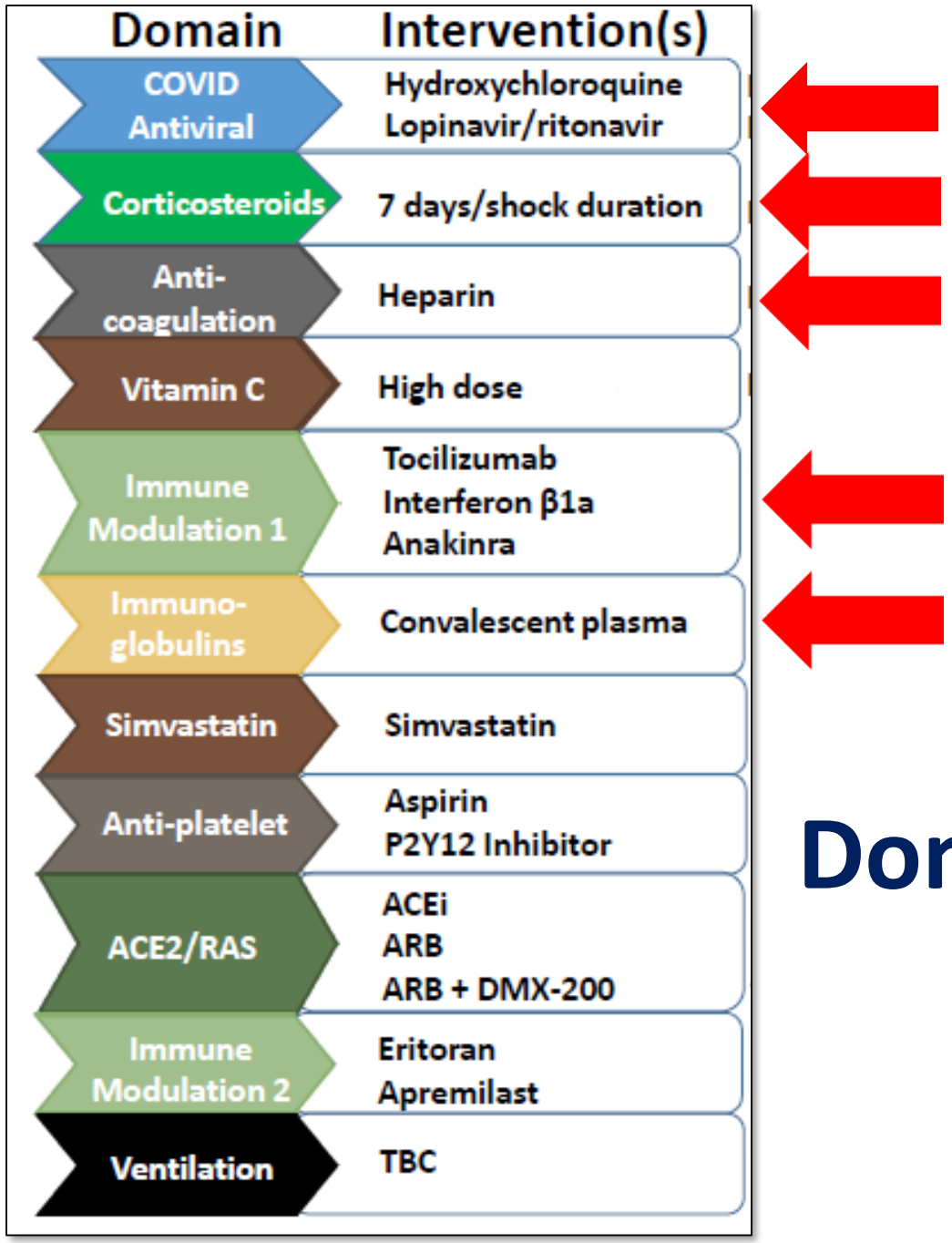
- **11,330 patients**
- **405 hospitals**
- **30 countries**



February 2, 2021

Randomized Embedded Multinational Adaptive Platform Trial

- **Sleeper trial in inter-pandemic period**
- **Multinational**
- **Studies multiple interventions**
- **Bayesian statistical design**
- **Response-adaptive randomization**
- **Focus is most severely ill patients**



Domain conclusions

Research

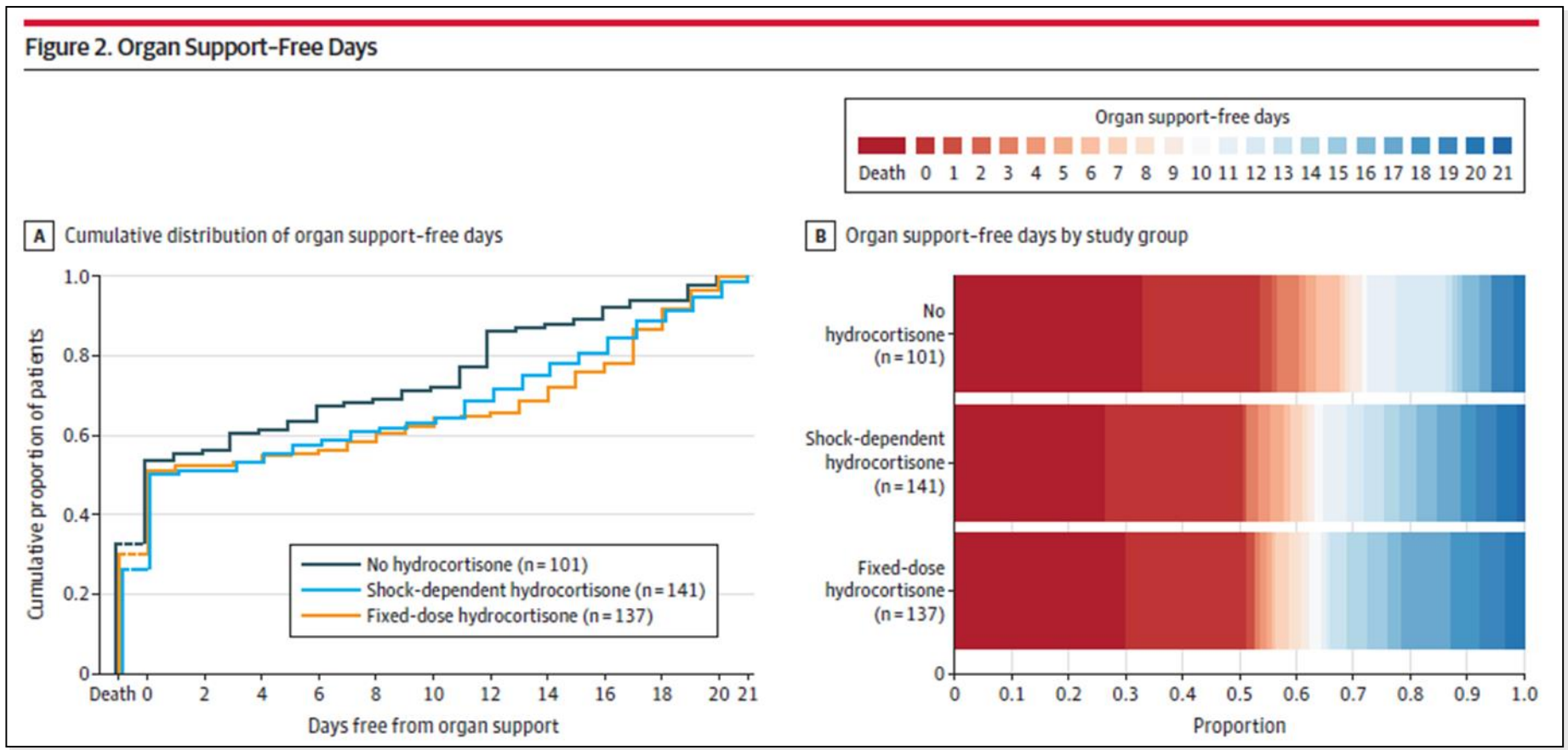
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

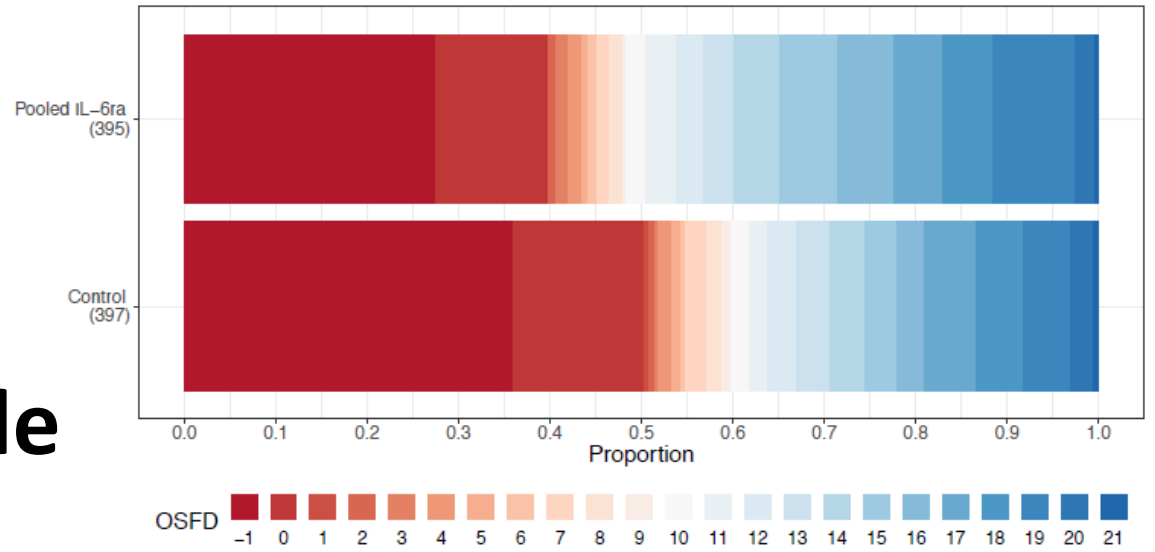
The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

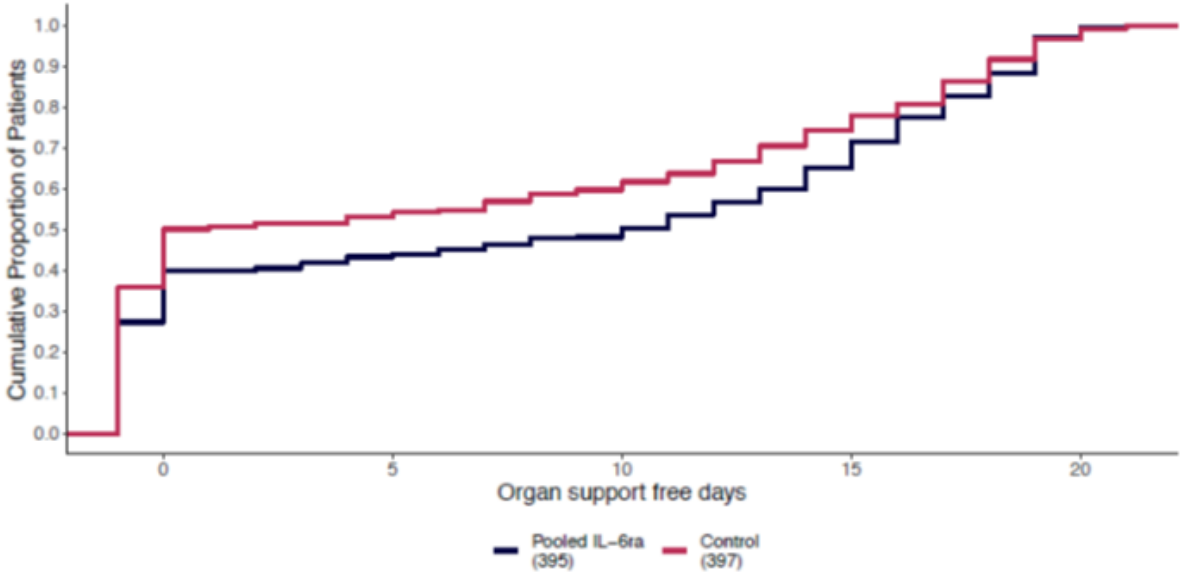
The Writing Committee for the REMAP-CAP Investigators

Figure 2. Organ Support-Free Days



Interleukin-6 Receptor Blockade





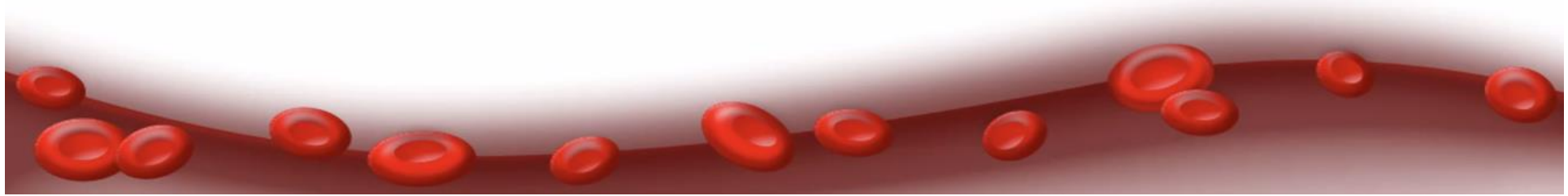
8.5% absolute mortality reduction

The Multiplatform RCT

ATTACC, REMAP, and ACTIV IV (NIH)

An international multiplatform RCT (mpRCT)

- Update:
  - December 18th, DSMB recommending stopping the severe state
    - ~1200 enrolled. Interim efficacy based on ~600 patients
  - Moderate state continues - ~2000 patients enrolled



Pre-publication interim data, not from a locked database and not peer reviewed

ATTACC, REMAP-CAP, and ACTIV IV-4a mpRCT

Primary outcome

State & D-dimer Strata	Proportional Odds Ratio Median (95% CrI)	Trial Statistical Conclusion
Moderate state, low D-dimer	1.57 (1.14 - 2.19)	**Superiority** [Probability of OR>1 = 0.997]
Moderate state, high D-dimer	1.53 (1.09 - 2.17)	**Superiority** [Probability of OR>1 = 0.991]
Moderate state, missing D-dimer	1.51 (1.06 – 2.15)	n/a⏃
Severe state	0.76 (0.60 – 0.97)	**Futility*** [Probability of OR>1.2 < 0.001]

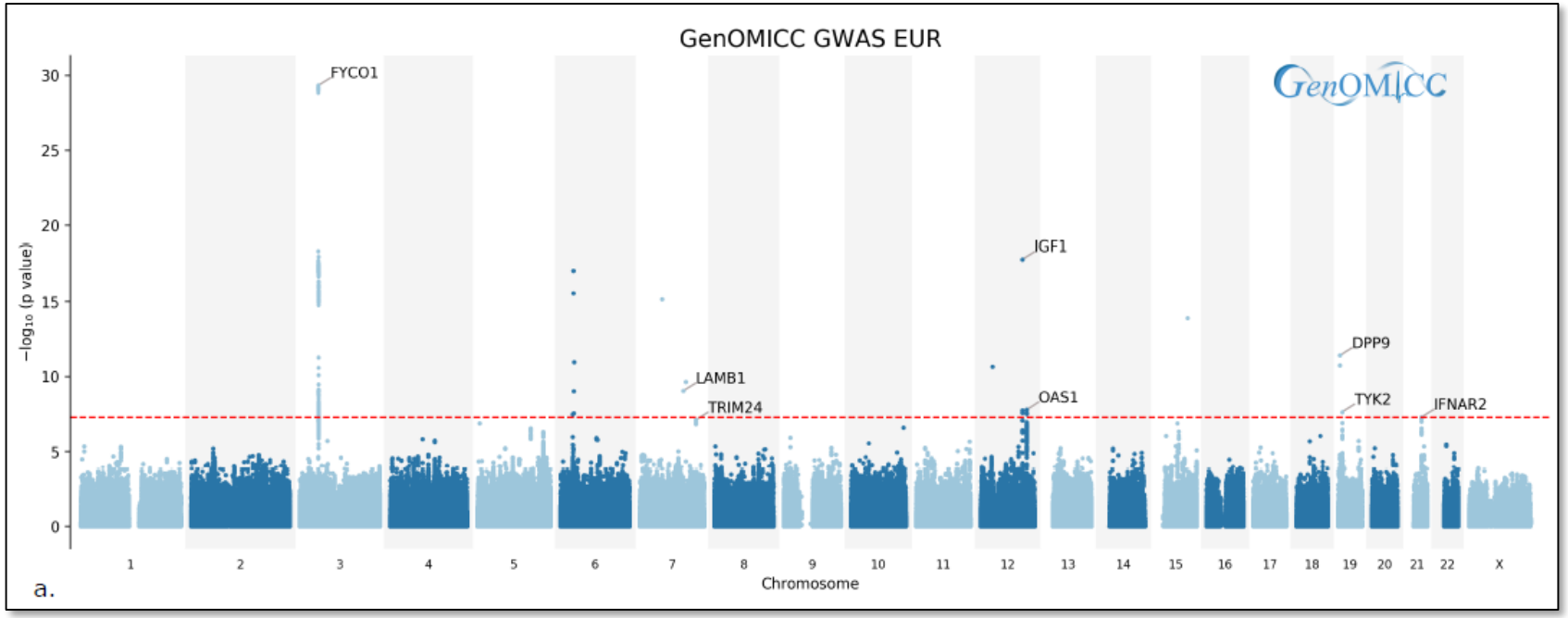
* Posterior probability of **inferiority** [Probability of OR<1 = 0.985]

⏃ Not evaluated for stopping at interim

OR >1 represents benefit. A higher OR occurs when either mortality is improved and/or if those who survive have reduced requirement for organ support

Release date: January 28, 202

GENETICS OF MORTALITY IN CRITICAL CARE



- New clinical trial models
- New mechanisms of data sharing

Can We Pool Data Across Trials to Accelerate Knowledge Generation?

- 7 clinical trials of corticosteroids for COVID-19
- Meta-DMC: Share interim data across trials
- Focus: Harm, futility
- Methods to be developed

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

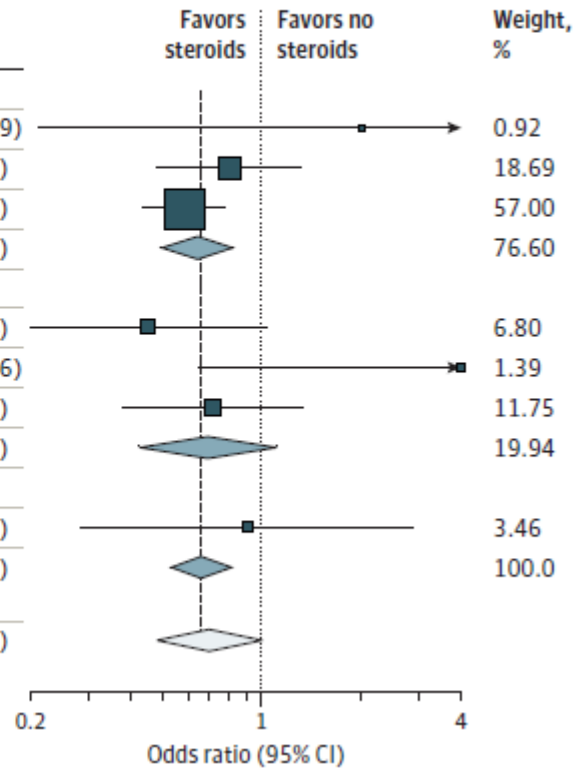
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19

A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



COVID-19 is Changing Clinical Research

- New trial designs
- International collaboration
- Acceptance of research as integral to clinical care
- New approaches to trial conduct and funding

Thank you!

William Osler Health System

niagarahealth
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How clinical studies enrolling critically ill COVID-19 patients from all ICUs can improve care

Ontario Critical Care Clinical Practice Rounds (OC3PR)

February 4, 2021

Alexandra Binnie, MD, DPhil, FRCPC

Intensivist, Critical Care Research Lead, William Osler Health System

Jennifer Tsang, MD, PhD, FRCPC, ABOM

Intensivist, Research Lead, Niagara Health

Associate Professor of Medicine, McMaster University

CCCTG
Canadian Critical Care Trials Group

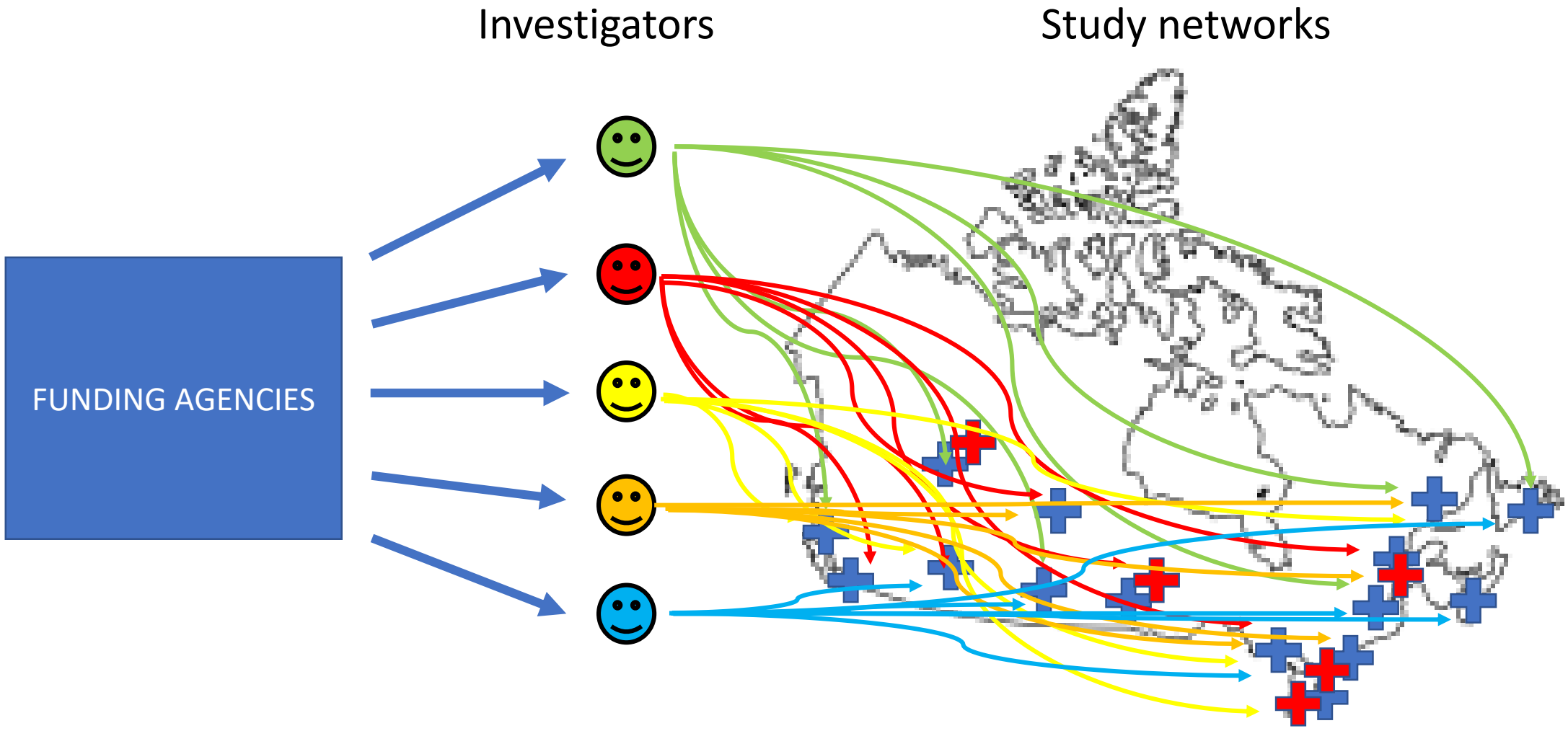
CCIRNet
Canadian Community ICU Research Network

Topics:

- How are ICU clinical trials organized in Canada?
- Why is community ICU participation in research low?
- How have community ICUs performed in COVID-19 research?
- Why should community ICUs consider participating in research?
- What are the models for community ICU research participation?

CCIRNet
Canadian Community ICU Research Network

How are ICU clinical trials organized in Canada?

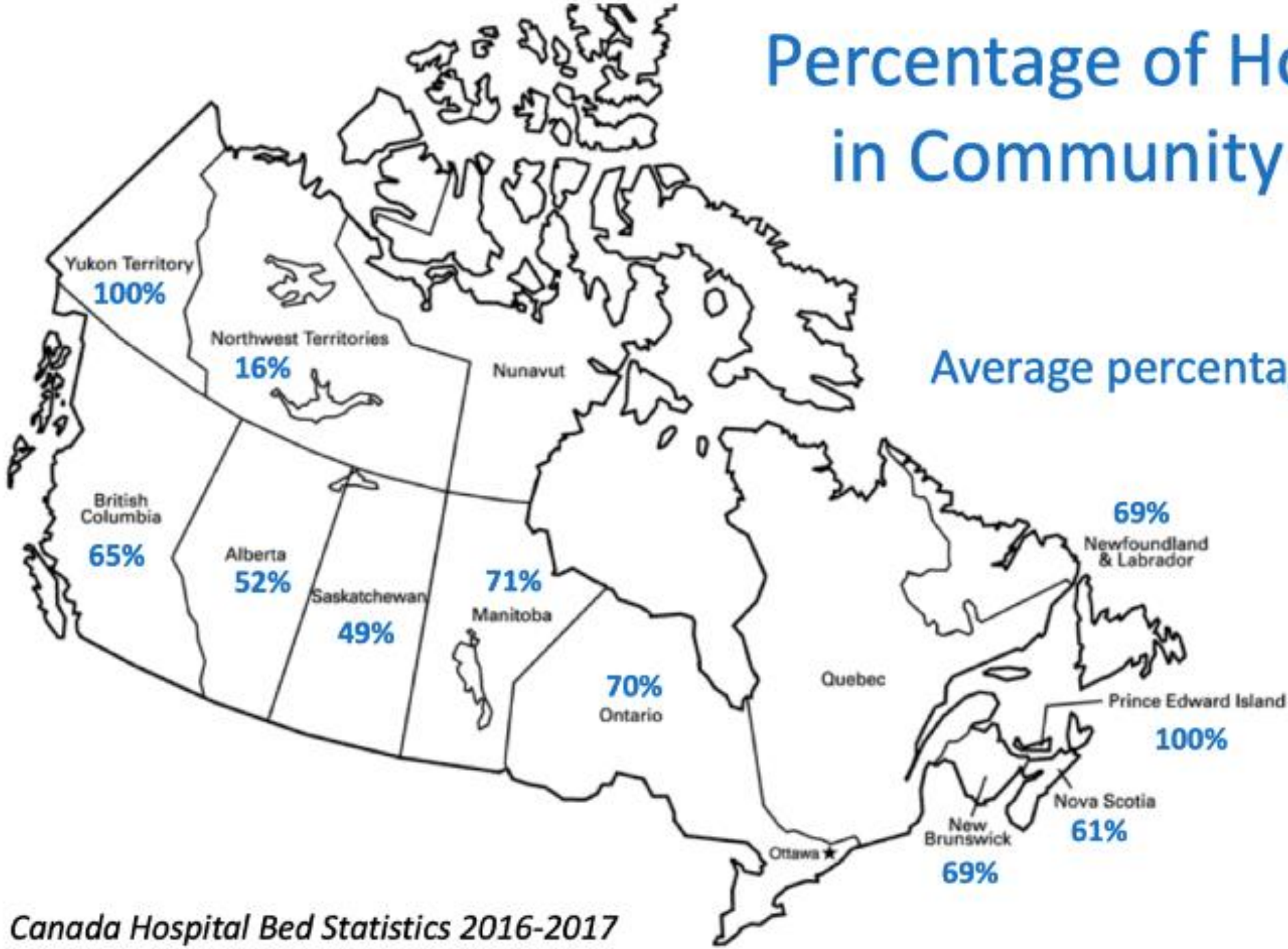


Each study builds its own network of sites, its own study procedures, its own documentation.

“Academic” vs “community” hospitals?

	“Academic “	“Community”
University Affiliation	Fully-affiliated	Most partially or not affiliated
Core Mandates	Research, teaching & health service delivery	Health service delivery
Location	Urban	Primarily suburban and rural
Contribution to total hospital beds in Canada	35%	65%
Contribution to ICU patient recruitment	~90%	~10%

Percentage of Hospital Beds in Community Hospitals



Average percentage in Canada = 65%

Canada Hospital Bed Statistics 2016-2017

Community ICU participation in PROSPECT

PRObiotics to prevent Severe Pneumonia and Endotracheal Colonization Trial

	Academic ICUs	Community ICUs
Total participating ICUs in Canada	34 (84%)	7 (16%)
Total patient enrolment	1,766 (87%)	189 (13%)
% urban hospitals	100%	14%
Mean age of participants	59.9 years	62.6 years *
Medical admission status	76.5%	93.7% *
ICU Mortality	21.2%	29.1% *

Tsang *et al.*, *ICME* 2019

What are the benefits of research participation?

- Faster patient recruitment and knowledge acquisition
- Greater inclusion of underrepresented patient populations
- Better generalizability of results
- Faster knowledge transfer
- Improved quality of care (locally and generally)
- Improved access to investigational medications/devices
- Greater connections between ICUs
- Improved career satisfaction for physicians, RNs, allied health

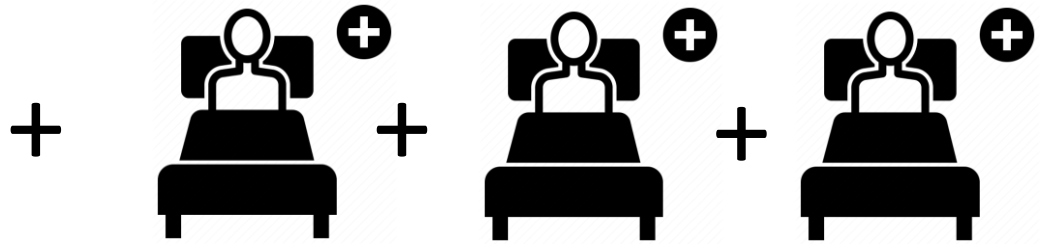
Reason for limited participation of community ICUS in clinical research

- Cultural – “not our role”
- Lack of incentives (financial or otherwise) for participation
- Lack of hospital research infrastructure (REB, contract review, research coordination, research pharmacy and laboratory)
- Lack of physician expertise
- Lack of mentoring
- Insufficient study funding to build and sustain a research program

How are ICU clinical trials funded in Canada?

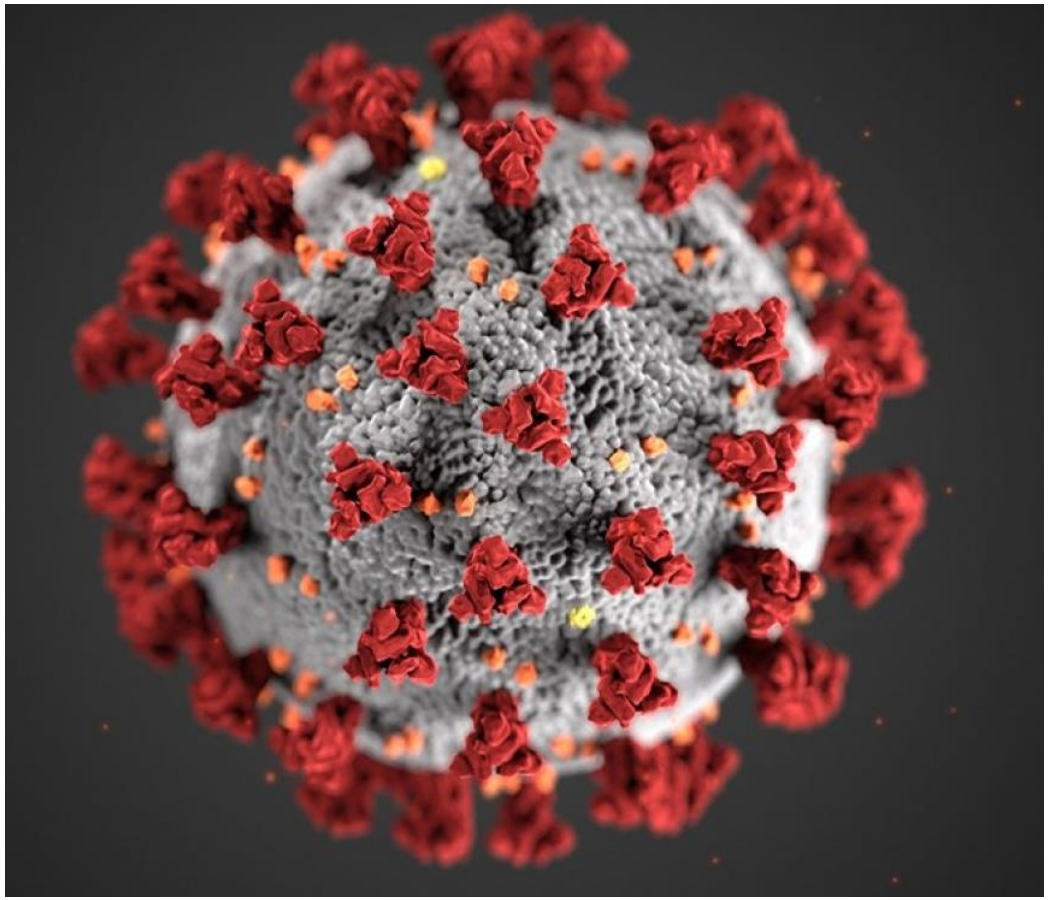
Study Centre

Start-up fee

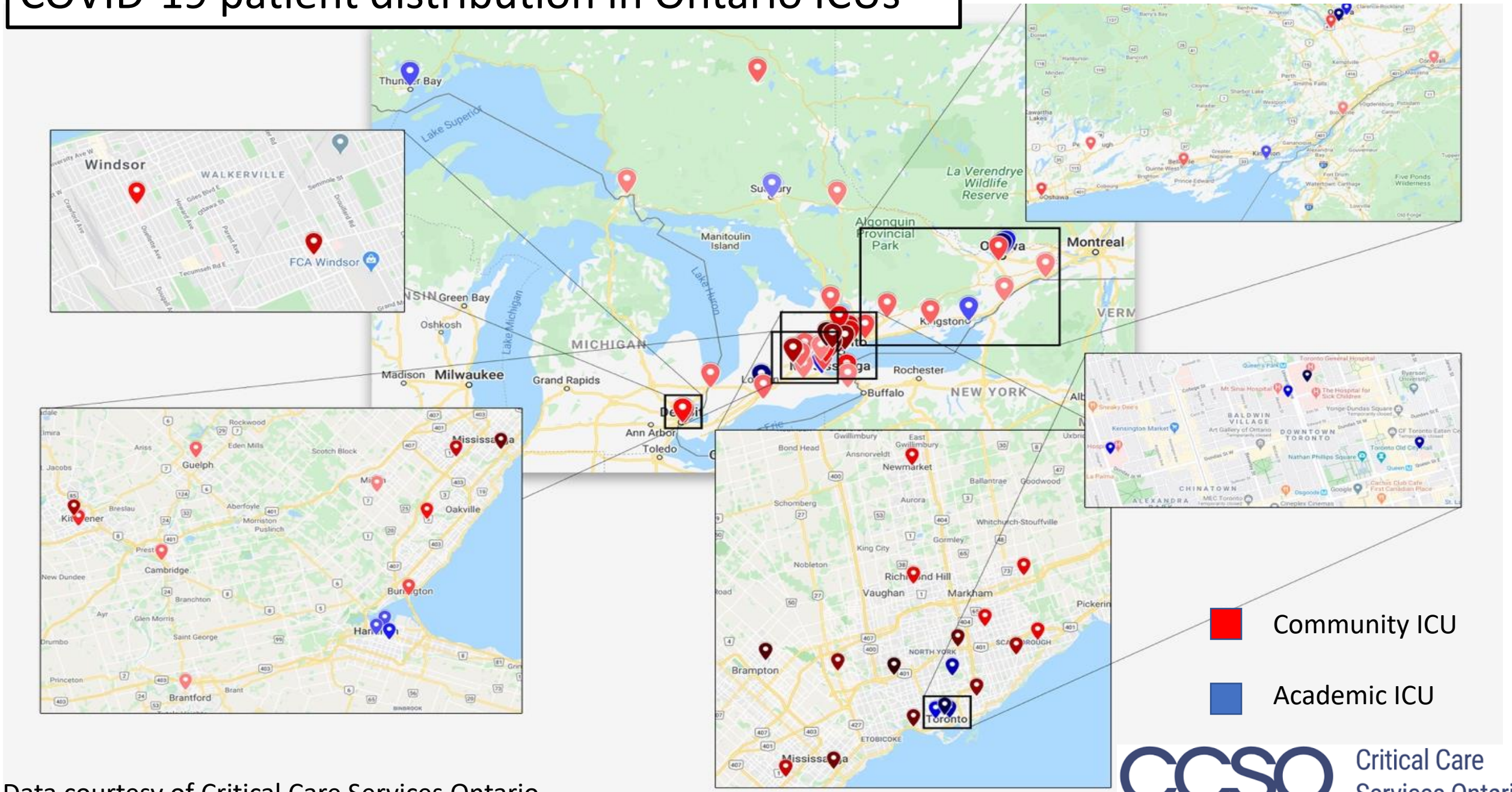


Per patient payments

2020: And then came COVID-19



COVID-19 patient distribution in Ontario ICUs



Data courtesy of Critical Care Services Ontario

CCSO Critical Care Services Ontario

COVID-19 in Ontario ICUs (April 16th, 2020)

Community ICUs

Color	Hospitals
	Welland General Hospital (Niagara Health System)
	North Bay Regional Health Centre
	Sault Area Hospital
	Brockville General Hospital
	Halton Healthcare Services Milton
	Brantford Community Healthcare system
	Cornwall-General Hospital
	Guelph General hospital
	Timmins and District Hospital
	Cambridge Memorial Hospital
	Peterborough Regional Health Centre
	Royal Victoria Regional Health Centre
	Quinte-Belleville Hospital
	St. Thomas Hospital
	BlueWater Sarnia
	Joseph Brant Hospital
	Lakeridge Health Corporation
	Queensway Carlton Hospital
	St. Mary's General Hospital

Color	Hospitals
	St. Catharines General Hospital (Niagara Health System)
	Halton Healthcare Services Oakville
	Windsor Regional Hospital Ouellette
	Mackenzie Health Hospital
	Markham Stouffville Hospital
	Scarborough Health Network Birchmount Hospital
	Scarborough Health Network Centenary Hospital
	Southlake Regional Health Centre
	Trillium Health Partners Credit Valley
	Windsor Regional Hospital Metropolitan
	Scarborough Health Network General Hospital
	Grand River Hospital
	Toronto East General Hospital
	William Osler Health System Etobicoke
	St. Joseph's Health Centre Toronto
	Trillium Health Partners Mississauga
	William Osler Health System Brampton Civic Hospital
	Humber River Hospital

Of the total number of ICU patients with COVID-19 on April 16 2020 in Ontario:

70% were in community ICUs

30% were in academic ICUs

Academic ICUs

Colour	Hospitals
	Health Sciences North
	Hamilton Health Sciences
	St. Joseph's Healthcare Hamilton
	Thunder Bay Regional Health Sciences
	Kingston General Hospital
	Montfort Hospital
	Juravinski Hospital
	Mount Sinai Hospital
	Toronto Western Hospital
	St. Michael's Hospital
	Sunnybrook Health Sciences Centre
	London Health Sciences Centre
	The Ottawa Hospital
	North York General Hospital
	Toronto General Hospital

Data courtesy of Critical Care Services Ontario

CCSO Critical Care Services Ontario

As of January 13th, 2021 community hospitals accounted for 75% of all COVID-19 patient-days in Ontario.

Ontario

COVID-19 studies Enrolling in Canada:

CATCO

Canadian Treatments for COVID-19

ACT

GenOMICC

REMAP-CAP

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

CONCOR-1

COVI-PRONE

ATTACC

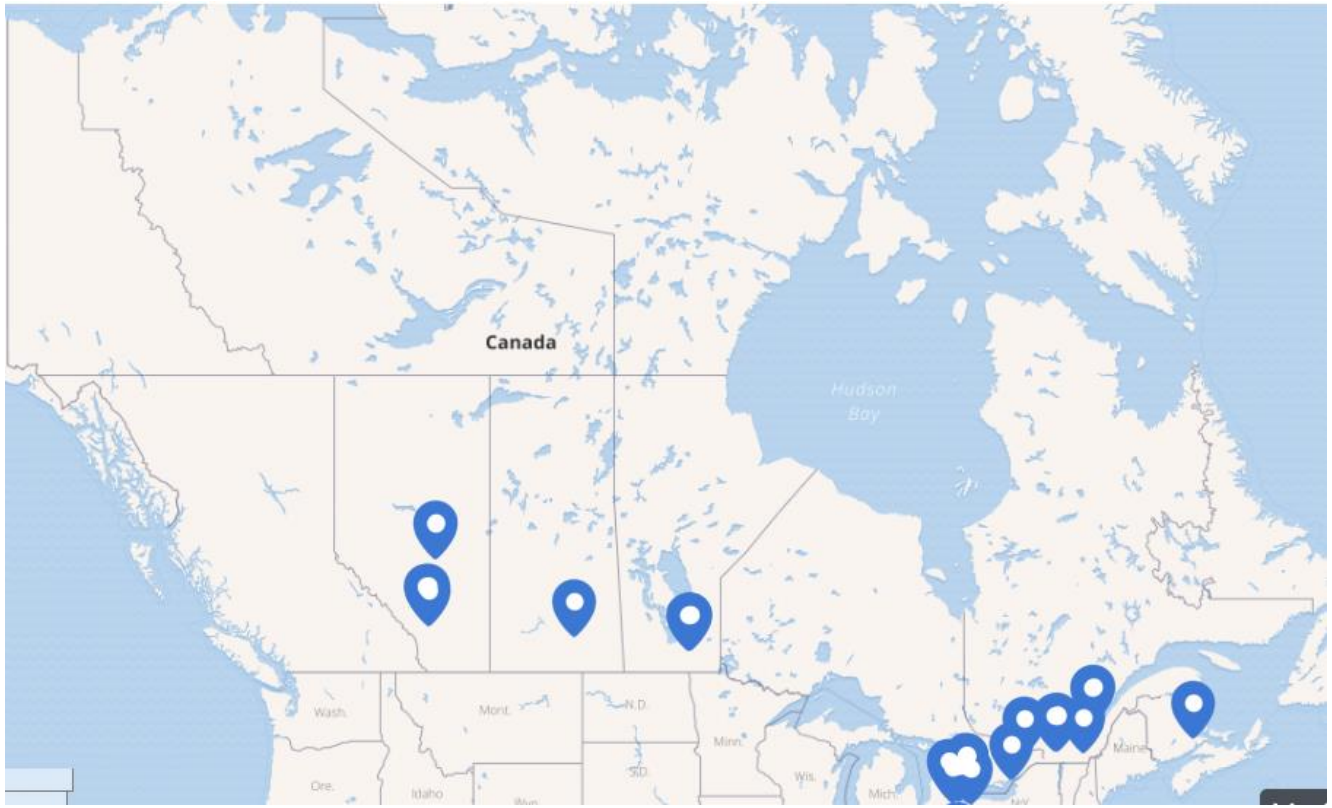
Lovit

Lessening Organ Dysfunction with VITamin C

Canadian community ICU enrollment in REMAP-CAP as of Jan 25th, 2021:

	REMAP-CAP (ICU)
Total ICU COVID-19 cases in Canada	7,089
Total study enrollment in Canada	144
Percentage of potential patients enrolled	2.0%
Number of academic centres	21 (75%)
Number of community centres	7 (25%)
Patients enrolled in academic centres	111 (77%)
Patients enrolled in community centres	33 (23%)

REMAP-CAP in Canada:



- Population: 37,000,000
- Adult ICUs: 319
- Adult ICU beds: 3,388

- REMAP-CAP sites: 29
- REMAP-CAP patients: 144
- % of global recruits: 2.7%

REMAP-CAP in the UK:

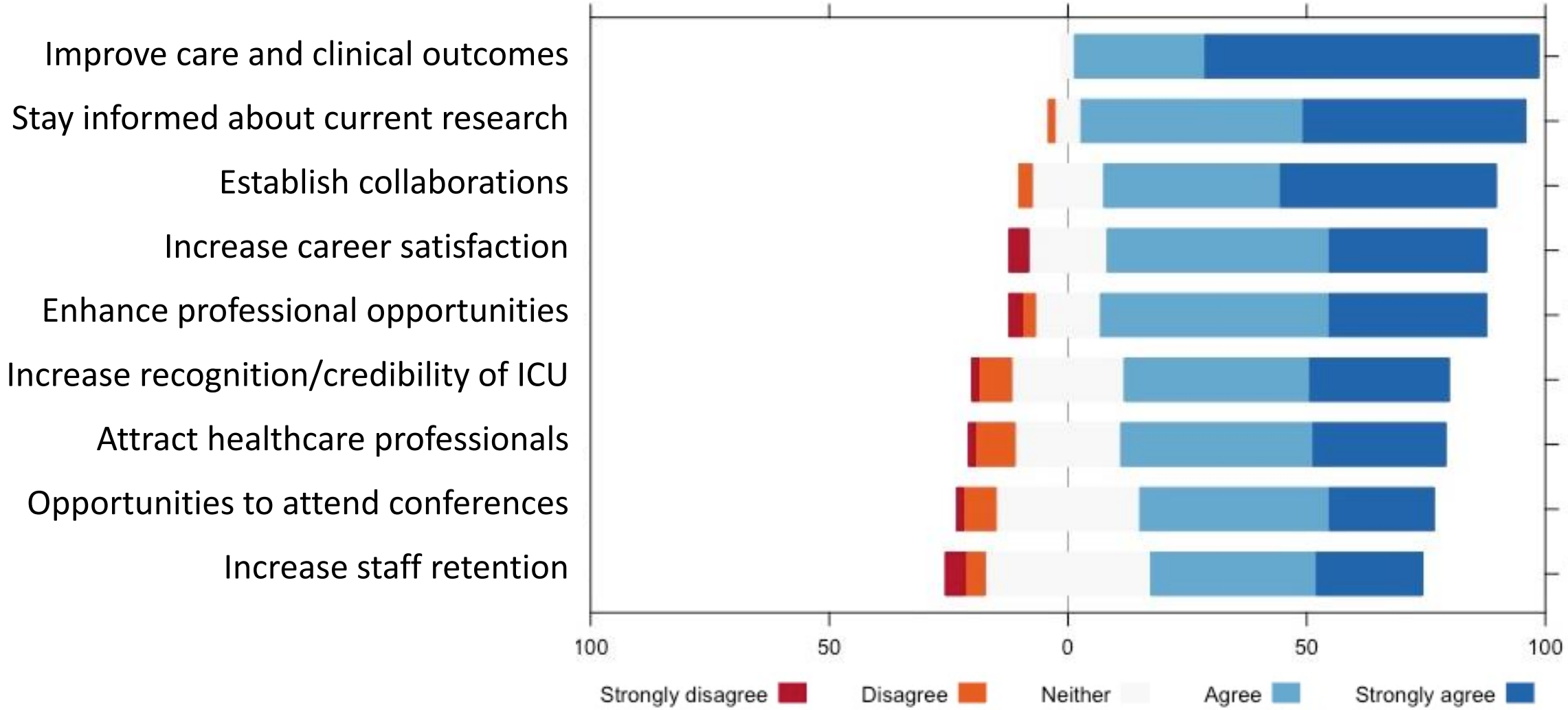
- Population: 67,000,000
- Adult ICUs: 285
- Adult ICU beds: 3,193

- REMAP-CAP sites: 142
- REMAP-CAP patients: 3,966
- % of global recruits: 76.1%

Reasons for low study enrolment in Canada:

- Limited research engagement amongst hospitals where the majority of COVID-19 patients receive their care
- Failure to integrate research into clinical practice
- Failure to prioritize research as part of high-quality clinical care
- Lack of research infrastructure
- Excess of clinical work
- Absence of incentives (financial or otherwise) to participate in research

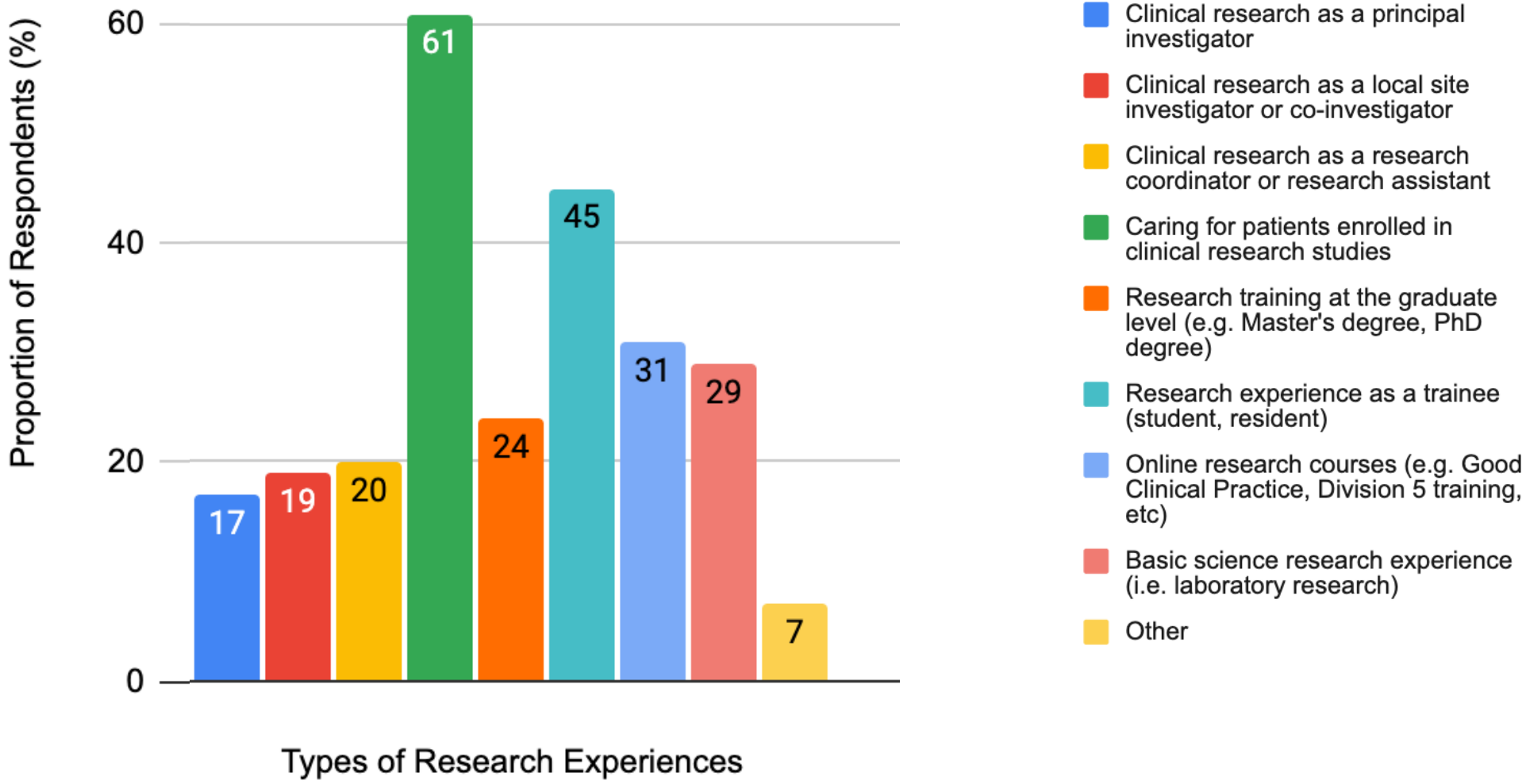
Community ICU survey: perceived benefits of COVID-19 research involvement



Pre-existing research infrastructure in Canadian community ICUs:

	% Community Hospitals
Pre-existing research program(s) in hospital	56%
Research policies and procedures	56%
Local research ethics board	50%
Pharmacy with research capability or experience	50%
Hospital research administration/office	39%
Research coordinator(s) or research assistants(s) in hospital	33%
On-site contract review capability	22%
Clinical laboratory department with research capability	11%
Diagnostic imaging department with research capability	11%

Community ICU survey: MD research experience



How enrolling in research studies can improve clinical care at your hospital:

- Increase speed of knowledge acquisition by shortening study durations
- Provide access to ”cutting-edge” therapies at your hospital
- Provide patients with the opportunity to participate in research
- Increase representation of ethnic, cultural, and socio-economic groups
- Improve generalizability of results
- Reduce off-label prescribing by physicians
- Accelerate knowledge transfer
- Align health system and health research priorities
- Improve connections between hospital departments (pharmacy, lab, DI)

Ontario community ICUs involved in research:

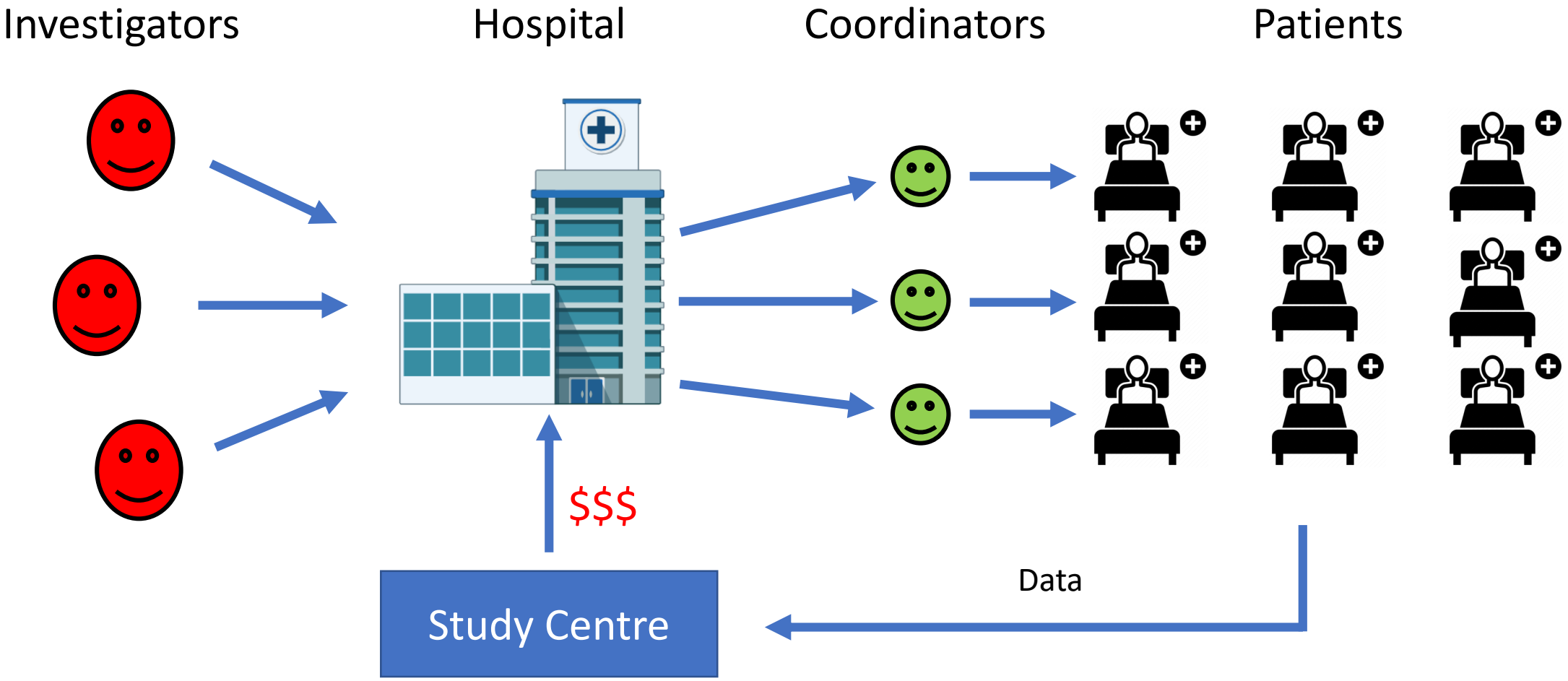
Pre-existing ICU research program	New research program
Brantford General Hospital (Brantford)	Trillium Health Partners (Mississauga)
Niagara Health (St Catharines)	Scarborough General Hospital (Toronto)
William Osler Health System (Brampton)	North York General Hospital (Toronto)
St Joseph's Health Centre (Toronto)	Royal Victoria Hospital (Barrie)
	Windsor Regional Hospital (Windsor)
	Grand River Hospital (Waterloo)
	Markham Stouffville Hospital (Markham)
	Lakeridge Health (Oshawa)
	Humber River Regional Hospital (Toronto)

William Osler Health System Research Program

- Community hospital system in suburban GTA (Brampton/Etobicoke)
  - Brampton Civic Hospital, Etobicoke General Hospital
- 38 level-3 beds, 10 level-2 beds
- MD physician group: 19 permanent staff, 4 locums
- Start of research program: 2017
- Research studies completed or in-progress to date: 10
- Number of research coordinators: variable (0.5 to 1.5)
- Recruitment in REMAP-CAP: 28 patients
- Recruitment in CATCO: 74 patients

William Osler Health System

William Osler Health System



Niagara Health Research Program

- Community hospital system in Niagara Region
  - St. Catharines Site
- 14 level-3 beds, 6 level-2 beds
- MD physician group: 9 permanent staff, 4 locums
- Start of research program: 2016
- Research studies completed or in-progress to date: 18
- Number of research staff: Research Coordinator (1xFTE), Research Assistant (1xFTE)
- Recruitment in REMAP-CAP: 14 patients
- Recruitment in CATCO: 17 patients

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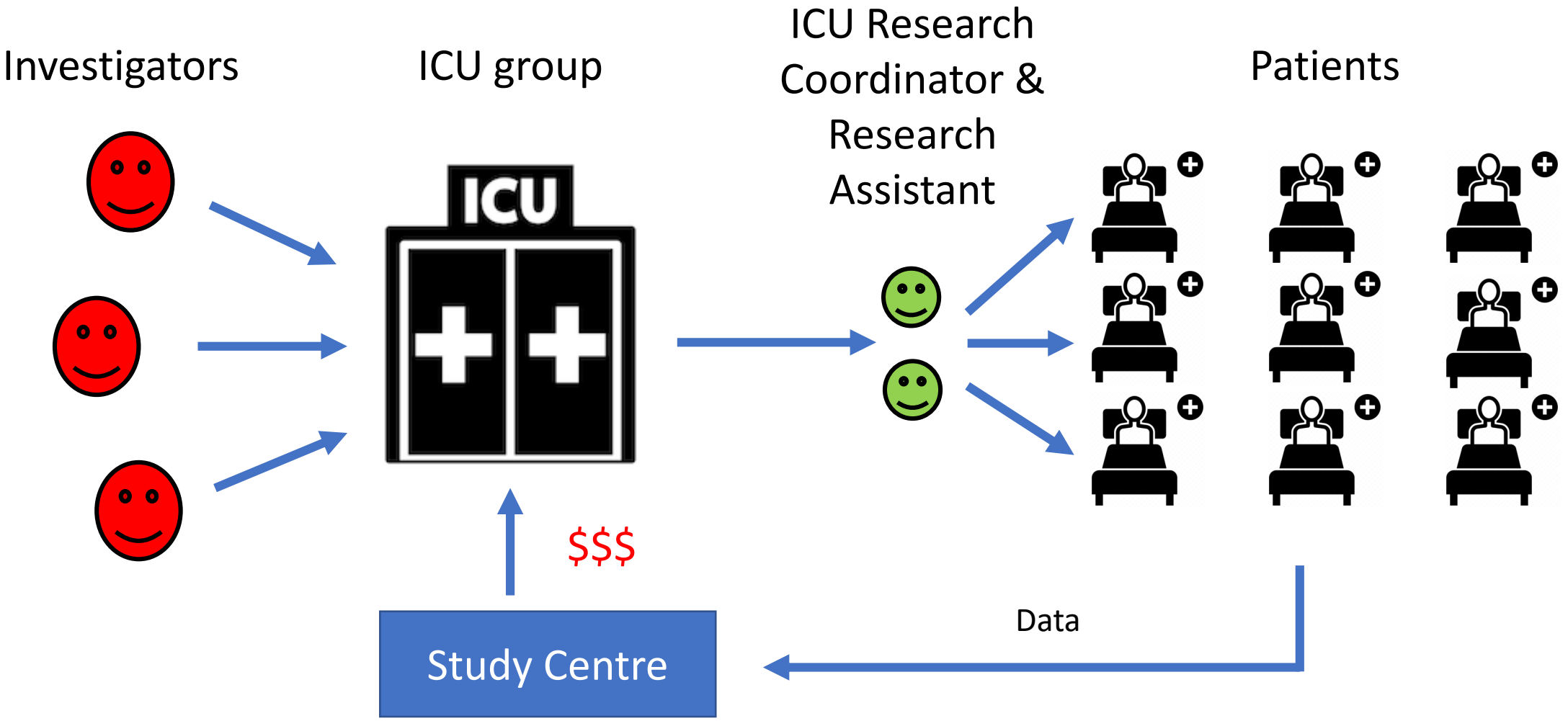
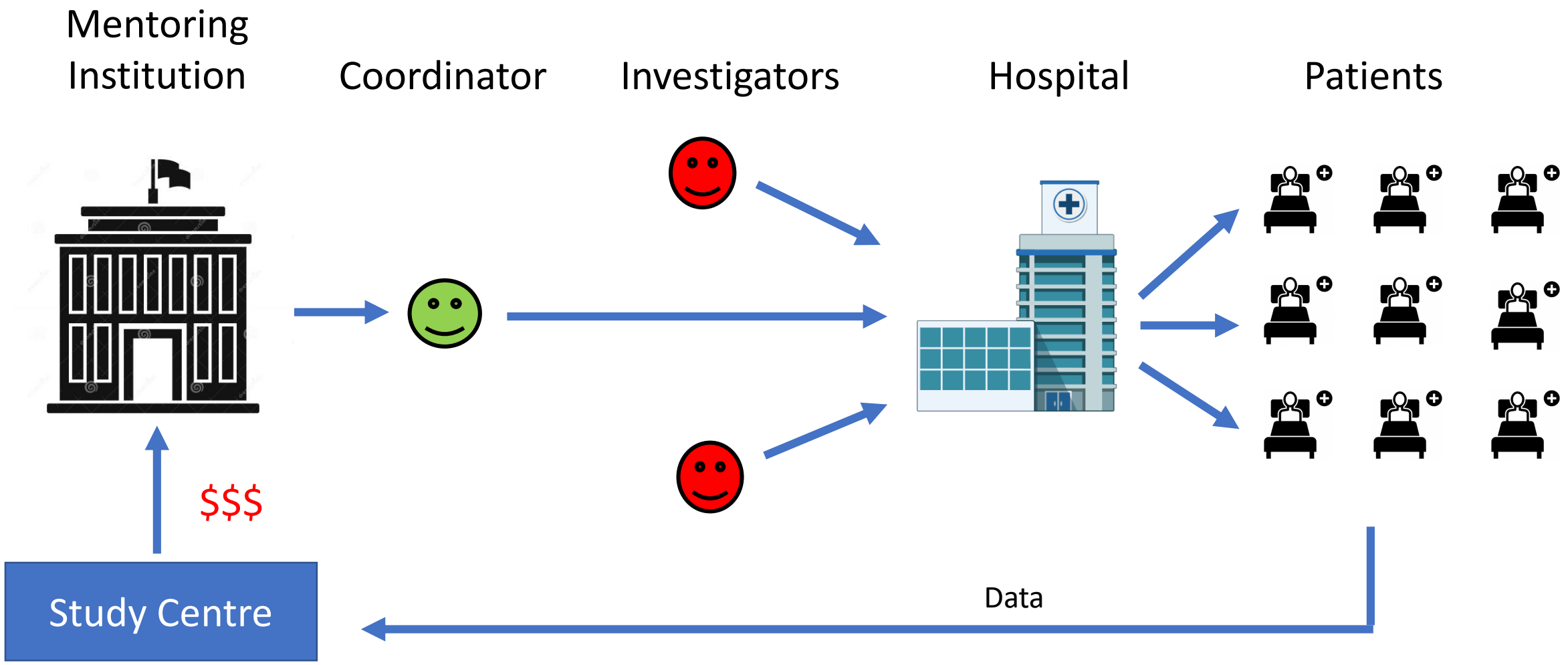
Niagara Health



Brant Community
HEALTHCARE SYSTEM

Brantford General Hospital



In Summary

- Most COVID-19 patients in Canada are cared for in hospitals that do not participate in clinical trials
- Canada's participation in COVID-19 studies has been low compared to the UK
- There are many potential benefits to conducting research in community ICUs:
  - Increased patient satisfaction, faster access to therapies,
  - Improved knowledge transfer and quality of care
  - Increased staff satisfaction, connections to other ICU groups and investigators
- Barriers to research participation exist but are surmountable

CCIRNet
Canadian Community
ICU Research Network

@CCIRNET

https://www.ccctg.ca/CCIRNet/About-CCIRNet.aspx

Email: CCIRNET@gmail.com

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the next topic?

Submit ideas in our evaluation survey (Link in chat)

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Feb 18 2021 at 2PM

Coagulation & COVID-19: What to Do?

Questions? **info@ccso.ca**

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