CYCLE RCT
Site Investigator Meeting

December 13, 2022 @ 5:00 – 6:00 pm EST
December 14, 2022 @ 9:00 – 10:00 am AEST (Melbourne)

Hosted by: Michelle Kho and the CYCLE Methods Centre

Agenda

1. Welcome and introductions
2. Review of CYCLE study question
3. Evidence update – TEAM RCT
4. Study updates
    - Safety Reports
    - Protocol Amendment
    - Enrolment
    - Data Cleaning and Validation
5. Manuscripts
6. Next steps

2. REVIEW OF CYCLE STUDY QUESTION

CYCLE: Critical Care Cycling to Improve Lower Extremity Strength

Research Question:

In medical-surgical ICU patients, does 30 minutes of in-bed cycling and routine PT started within the first 4 days of mechanical ventilation, compared to routine PT improve patient function at 3 days post-ICU?

McMaster University HEALTH SCIENCES

CCCTG Canadian Critical Care Trials Group

CIHR IRSC

Rationale for CYCLE

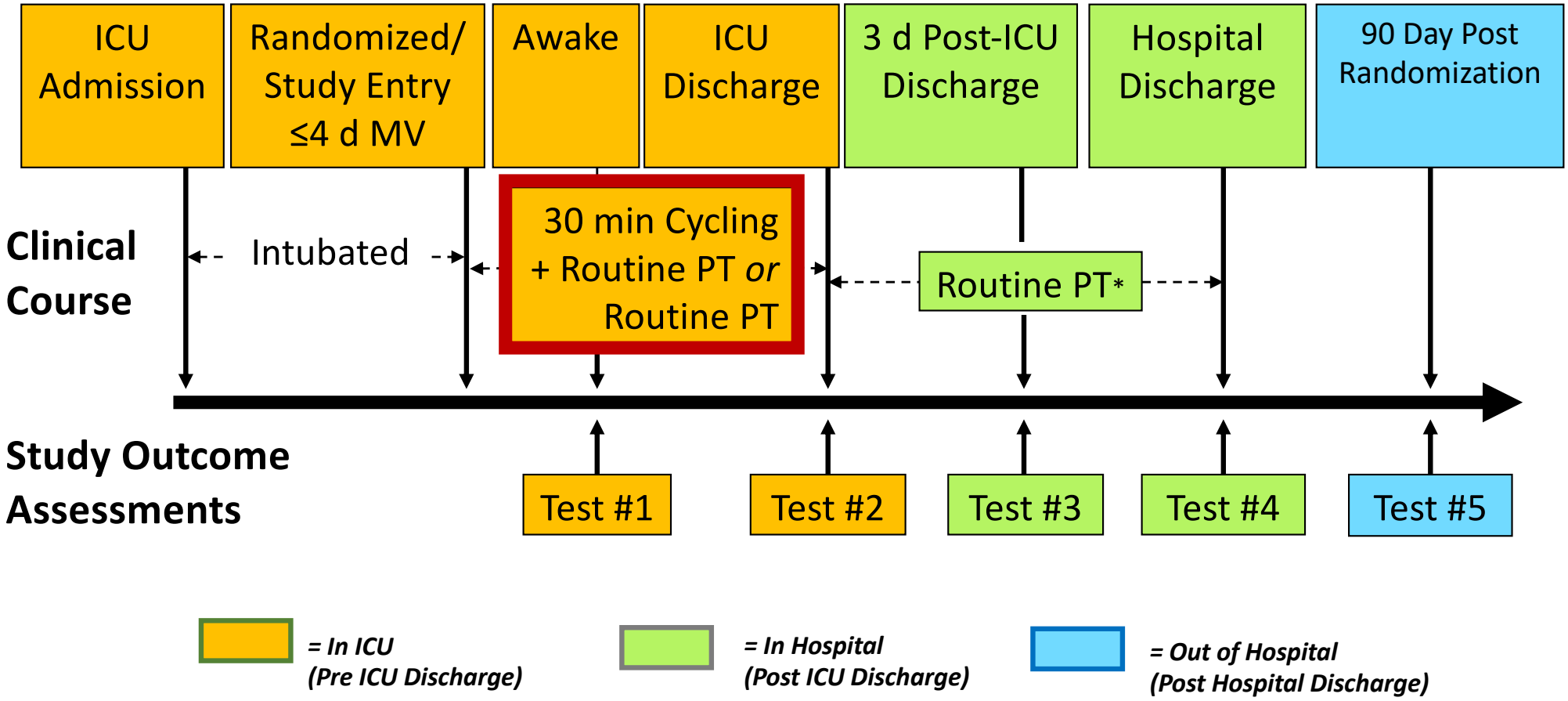
- **RCT:** PT and OT started within 1.5 days of intubation improves independence at hospital d/c[1]
  - Main difference: 19.2 minutes/ day during MV
- **RCT:** In-bed cycling started ICU day 14 improved 6-minute walk test distance at hospital discharge[2]
- **Observational study:** Main barriers to mobility are presence of ETT and sedation[3]
- **Question:** Can we initiate in-bed cycling with patients *earlier* in their ICU stay, and will it improve patient outcomes?

[1]Lancet. 2009. 373:1874-1882. [2]Crit Care Med. 2009.37(9):2499-2505. [3]Crit Care.2015.19:81.

CYCLE

- **Design:** 360 patient, multicenter, international open-label randomized trial
- **Population:** Medical-surgical adults within the first 4 days of mechanical ventilation
- **Intervention:** 30 minutes/ day of in-bed cycling + routine physiotherapy
  - **Until ICU discharge, 28 days, or able to march on the spot for 2 consecutive days, whichever comes first**
- **Comparison:** Routine physiotherapy
- **Primary Outcome:** Physical Function ICU Test @ 3 days post-ICU discharge by blinded outcomes assessors

CYCLE RCT Study Schema



Cycling will occur **until ICU discharge, to a maximum of 28 days**, or the patient is able to march on the spot for **2 consecutive days**, whichever occurs first.

3. EVIDENCE UPDATE – TEAM RCT

ORIGINAL ARTICLE

Early Active Mobilization during Mechanical Ventilation in the ICU

The TEAM Study Investigators and the ANZICS Clinical Trials Group*

N Engl J Med 2022; 387:1747-1758

DOI: 10.1056/NEJMoa2209083

Research Question: In mechanically ventilated adults, does early, goal-directed mobilization compared to usual care improve # days alive and out of hospital by day 180?

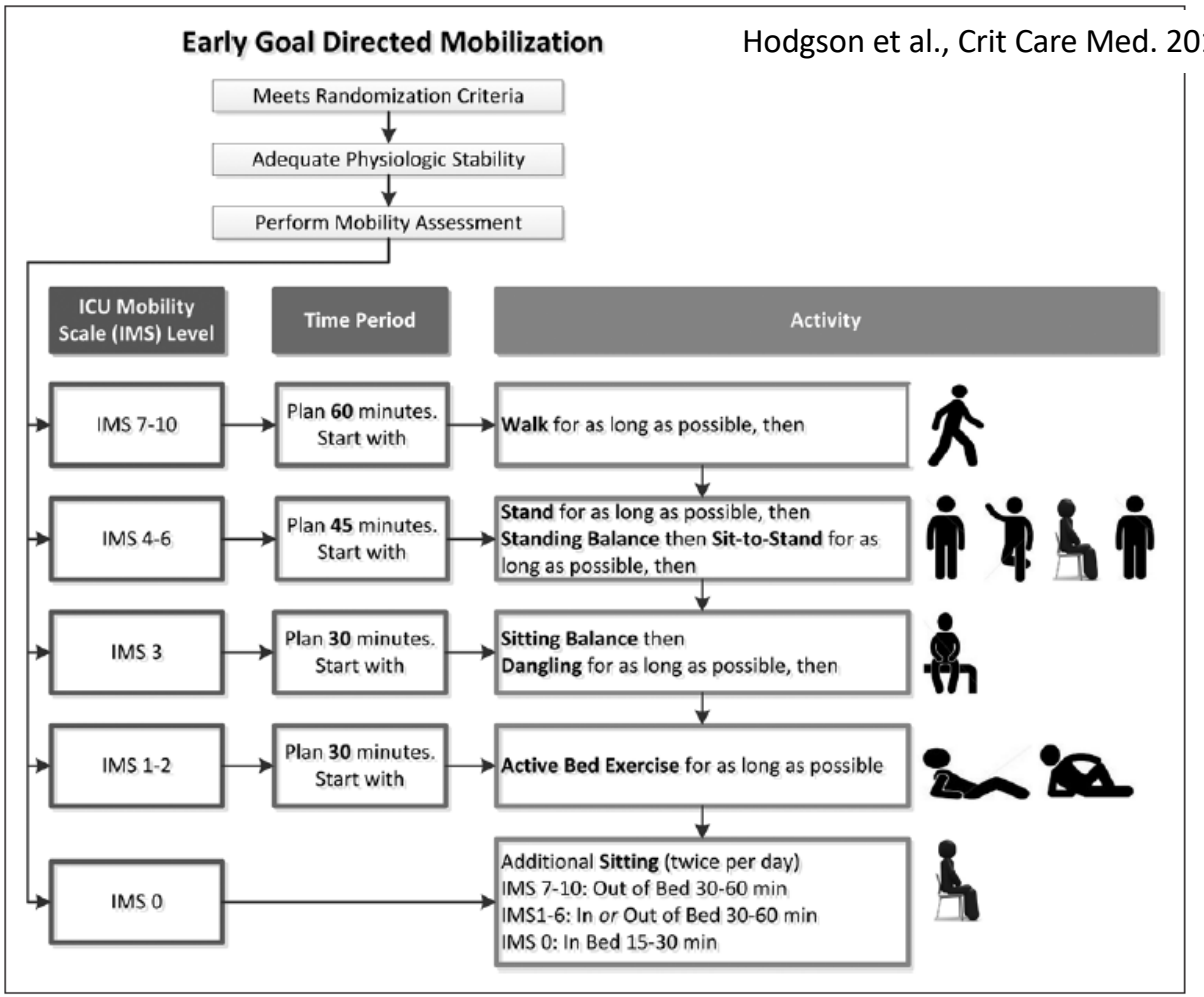
PICOS

- **Population**: Mechanically ventilated adults in ICU who were expected to undergo at least 1 additional day of mechanical ventilation
- **Intervention (unblinded)**: Minimization of sedation as required, daily physiotherapy (7 days per week), individually tailored to achieve the highest possible level of mobilization provided for as long as possible before a step-down to lower levels of activity if the patient became fatigued
- **Comparison (unblinded)**: Usual Care
- **Outcome**: # days alive and out of hospital by day 180
- **Study design**: Randomized controlled trial in 49 centres and 6 countries

TEAM Intervention

TEAM

Start with highest level of activity, then titrate down



Hodgson et al., Crit Care Med. 2016 Jun;44(6):1145-52.

Figure 1. Early goal-directed mobilization algorithm. Once randomized and physiological stability is achieved, the mobility team assessed the ICU mobility scale (IMS) and targeted exercise at the highest possible level of the IMS for as long as possible.

Start with lower level of activity, then titrate up

Other ICU Rehab studies

ORIGINAL ARTICLE

Early Active Mobilization during Mechanical Ventilation in the ICU

The TEAM Study Investigators and the ANZICS Clinical Trials Group*

N Engl J Med 2022; 387:1747-1758

- ✓ Largest ICU rehabilitation study in the field – 750 patients!
- ✓ Multi-centre, multi-national
- ✓ High consent rate – 91%
- ✓ 7 days per week physiotherapy
- ✓ 6-month follow-up for physical function, cognition, psychological distress
- ✓ Patient-reported outcomes blinded


ORIGINAL ARTICLE

Early Active Mobilization during Mechanical Ventilation in the ICU

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Conclusions (authors)

N Engl J Med 2022; 387:1747-1758

- No difference in number of days alive and out of hospital @ 180 days between early goal-directed mobilization than usual care
- Intervention associated with increased adverse events

What outcomes do we measure and when?

<u>Consider</u>:

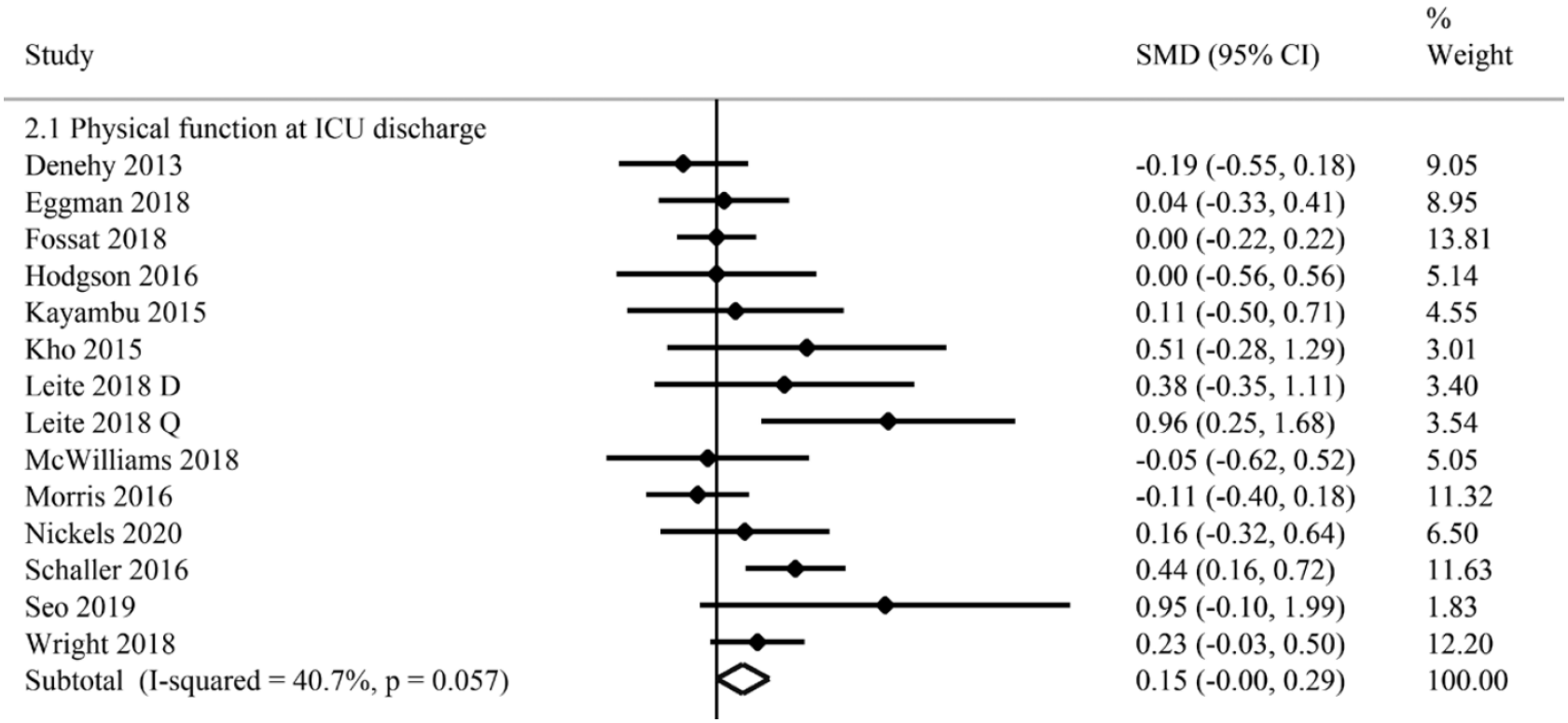
- Proximity of primary outcome to treatment intervention
- Confounding post-ICU
- Time to muscle weakness

REVIEW ARTICLE

Physical Rehabilitation in the ICU: A Systematic Review and Meta-Analysis

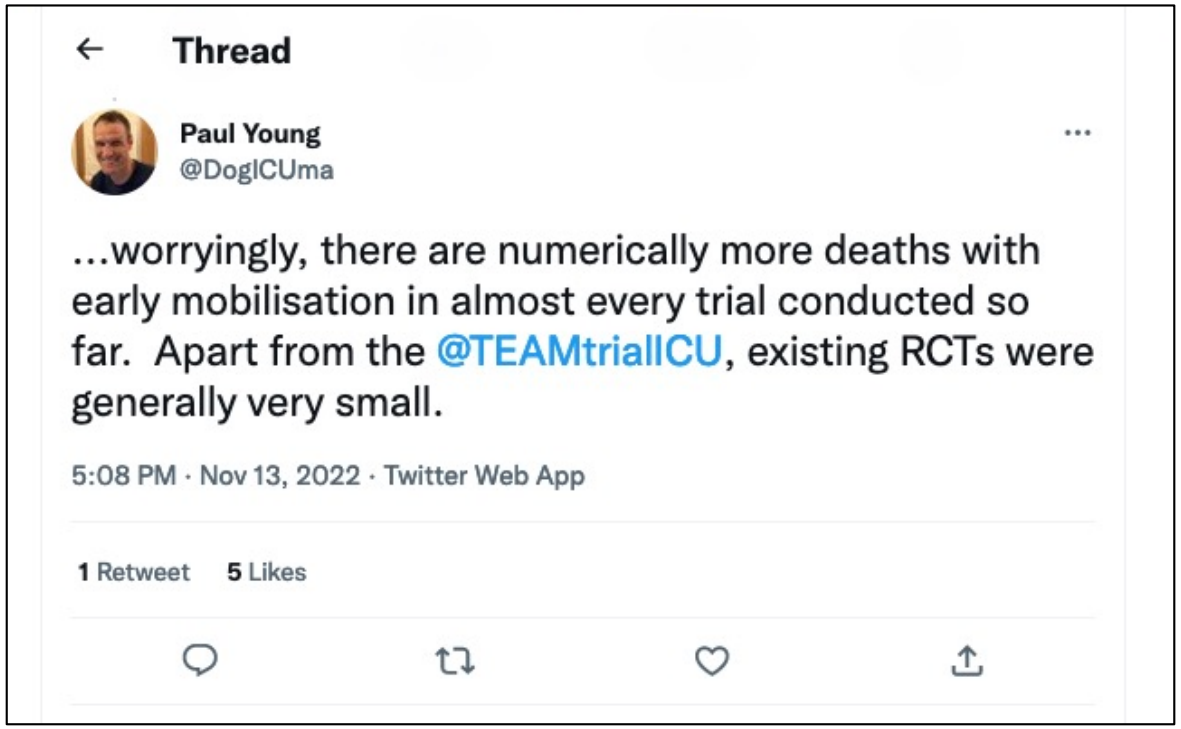
Physical function at ICU discharge *favours* early rehabilitation

Wang et al., Crit Care Med. 2022. 50(3):375-388.



0.15 (0, 0.29)

Increased mortality?



Consider:

- Totality of evidence
- Baseline mortality rate
- Need for an updated systematic review

Physical Rehabilitation in the ICU: A Systematic Review and Meta-Analysis

Wang et al., Crit Care Med. 2022 Mar 1;50(3):375-388

Time point	Study	N	Intervention n (%)	Control n (%)	
ICU Discharge	Wang et al. 2022	2,752	215/1,379 (15.6)	207/1,373 (15.1)	30 studies
28-day mortality	TEAM	741	58/371 (15.6)	41/370 (11.4)	
Hospital discharge	Wang et al. 2022	3,143	244/1,567 (15.5)	250/1,576 (15.9)	26 studies
	TEAM	Not reported	Not reported	Not reported	
6 months	Wang et al. 2022	1,373	193/684 (28.2)	187/689 (27.1)	9 studies
180 days	TEAM	741	83/371 (22.5)	71/370 (19.5)	

ICU rehabilitation and adverse events

<u>Consider</u>:

- What was the Adverse event?
- A-priori (*Severe* adverse events) or other (adverse events)?
- When did the events occur?
- What were the consequences?
- Risks of reporting bias
  - Over-report in intervention
  - Under-report in comparison

Research

Serious adverse events in academic critical care research

Deborah Cook MD, François Lauzier MD, Marcelo G. Rocha MD, Mary Jane Sayles RN, Simon Finfer MD

CMAJ. 2008. 178(9): 1181-1184.

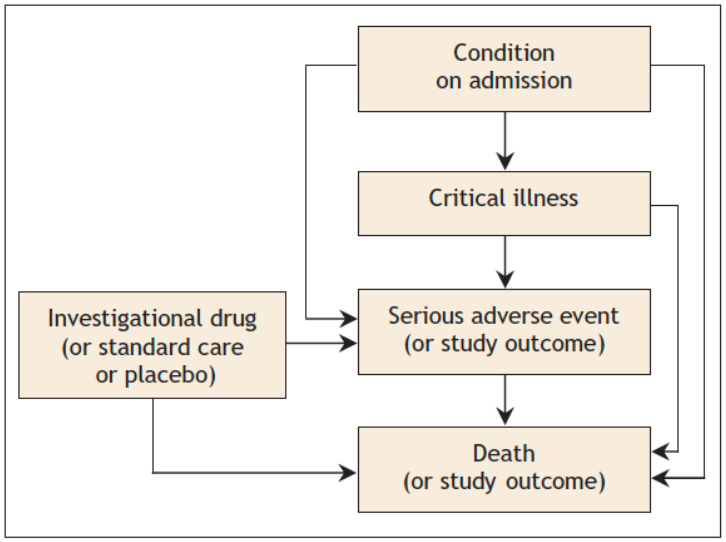


Figure 1: Possible relationships between the condition on admission, a patient's critical illness, the study drug, serious adverse events and death in academic trials of drugs in common use in critical care.

Challenges:

1. Variable definition and reporting
2. Interpretation in light of natural history of critical illness
3. Attribution to the drug/ intervention being tested
4. Attribution of death to serious adverse events
5. Interpretation of serious adverse events by REBs

Safety of Patient Mobilization and Rehabilitation in the Intensive Care Unit

Systematic Review with Meta-Analysis

Peter Nydahl[1*], Thiti Sricharoenchai[2*], Saurabh Chandra[3], Firuzan Sari Kundt[4], Minxuan Huang[5], Magdalena Fischill[6], and Dale M. Needham[7]

Nydahl et al., Ann Am Thorac Soc Vol 14, No 5, pp 766–777, May 2017

48 papers /
43 studies

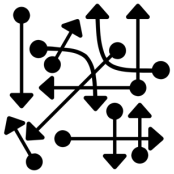
7,456
patients

Events *measured* in 52% - 69%

- Hemodynamic changes
- Desaturation
- IV catheter removal
- ETT removal
- Fall
- Cardiac arrest
- Other tube removal
- Other

2.6% sessions
583/ 22,351

97.4%
sessions no
events



17 safety
definitions

Different
activities

sessions

Desaturation
1.9/1,000

Hemodynamic
3.8/1,000

IV catheter
removal

TEAM STUDY QUIZ

4. CYCLE STUDY UPDATES

SAFETY REPORTS

DMC Meeting September 2020

DMC Members:

Dr. Eleanor Pullenayegum (chair), Dr. Marc Moss, Dr. Nicholas Hart

Reporting:

- Adverse events every 6 months
- Severe adverse events reported within 24 hours
  - **Cardiac arrest** or **unplanned extubation** directly related to the study protocol as assessed by the the site PI

Emergency DMC meeting triggers:

1. Adverse events/ serious adverse events
2. New external evidence
3. Major events that impact study protocol or study completion

Internal site plan for communicating SAEs to Methods Centre

Safety Report Timeline – CYCLE RCT

Initial Meeting DMC & Methods Centre	Jul-07-2020	• DMC membership confirmation • Defining AEs & SAEs and confirming reporting metrics/variables • Establish timelines for subsequent meetings/triggers for calling emergency meetings
1st Safety Report (Interim Analysis)	Sep-29-2020	• 180 patients (as of Feb-21-2020) • No safety or ethical concerns, approved to proceed as planned
2nd Safety Report	Mar-12-2021	• 231 patients (as of Dec-31-2020) • No safety or ethical concerns, approved to proceed as planned
3rd Safety Report	Sep-13-2021	• 254 patients (as of Jun-30-2020) • No safety or ethical concerns, approved to proceed as planned
4th Safety Report	Mar-10-2022	• 281 patients (as of Dec-31-2021) • No safety or ethical concerns, approved to proceed as planned
5th Safety Report	Sep-09-2022	• 305 patients (as of June-30-2022) • No safety or ethical concerns, approved to proceed as planned

No SAEs (cardiac arrests or unplanned extubations) attributed to routine PT/rehab or in-bed cycling, to date

PROTOCOL AMENDMENT

Protocol Amendment

Approved by Clinical Trials Ontario, October 10, 2022

Summary of changes:

1) Expanded the type of personnel to complete in-bed cycling with patients beyond physiotherapists to now include ”delegate”

- Implementation on a site-by-site basis
- Requirements for the trial do not change

2) Extended anticipated enrolment period

- 7/2018 to 3/2023 (previously 7/2018 to 3/2021)

3) Added information on virtual training sessions

- Due the COVID-19 pandemic, we will also offer virtual training sessions and refresher sessions per institutional requirements.

Contract Extension Execution Status - CYCLE RCT

	Status as of: Dec-12-22
Sent to McMaster Agreements Officer	14/15 (93.3%)
Signed (Principal Investigator)	13/15 (86.7%)
Signed (Local Site)	13/15 (86.7%)
Fully Executed	13/15 (86.7%)

Amended Consent Form Submission Status - CYCLE RCT

Site	Local REB – Submitted	Local REB – Approved
St. Joseph's, Hamilton	No	No
Juravinski, Hamilton	No	No
Hamilton General	No	No
St. Michael's, Toronto	No	No
Mount Sinai, Toronto	N/A	N/A
Duke, USA	Unknown	Unknown
University of Maryland, USA	Yes	Yes
Ottawa Civic	No	No
Ottawa General	No	No
Austin Health, Australia	Unknown	Unknown
Montreal Sacre Coeur, Quebec	Unknown	Unknown
Sherbrooke, Quebec	Yes	Yes
Kingston General	Yes	Yes
Brantford General	Unknown	Unknown
London, Victoria	No	No
Niagara Health, St. Catharines	Yes	No
Hotel Dieu de Levis, Quebec	Unknown	Unknown

Data as of December 13, 2022

TRAINING

Site Training/Update Meetings (Post-Interim Analysis, Sep-29-2020)

	Start-up		Refresher	
	Meetings (#)	Staff Trained (#)	Meetings (#)	Staff Trained (#)
Research Coordinator	6	19	N/A	N/A
Interventionist	7	29	8	41
Physical Outcomes	10	35	8	59
TOTAL	**23**	**83**	**16**	**100**

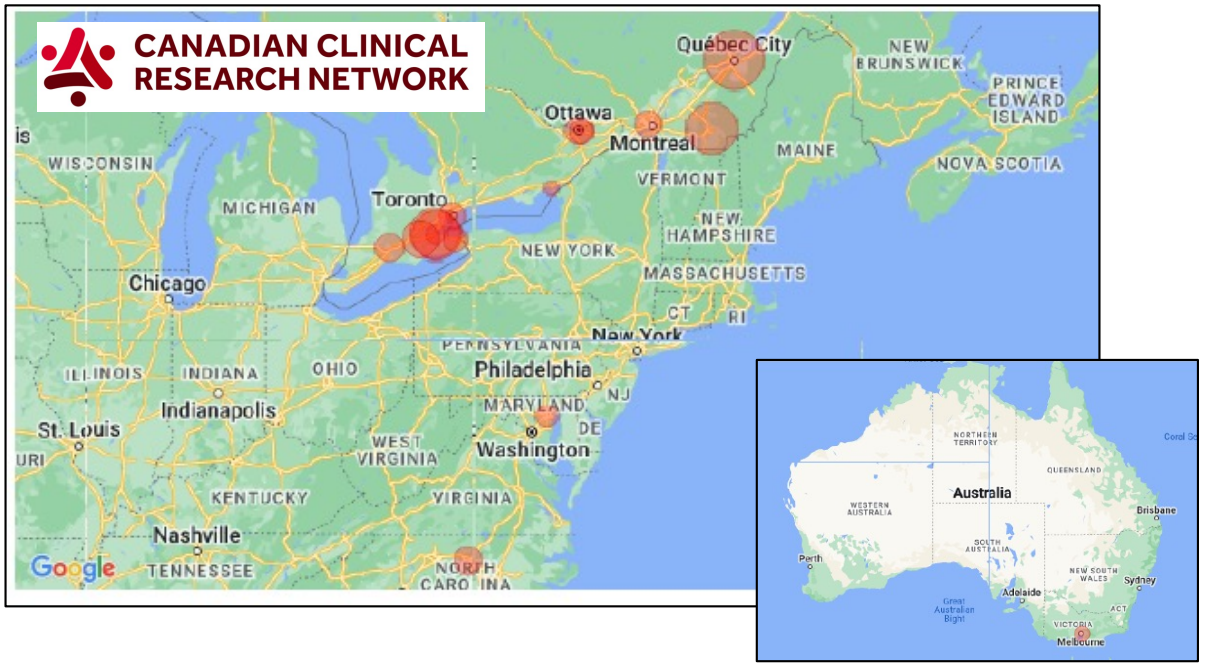
	Meetings (#)
PI + RC Update	12

ENROLMENT

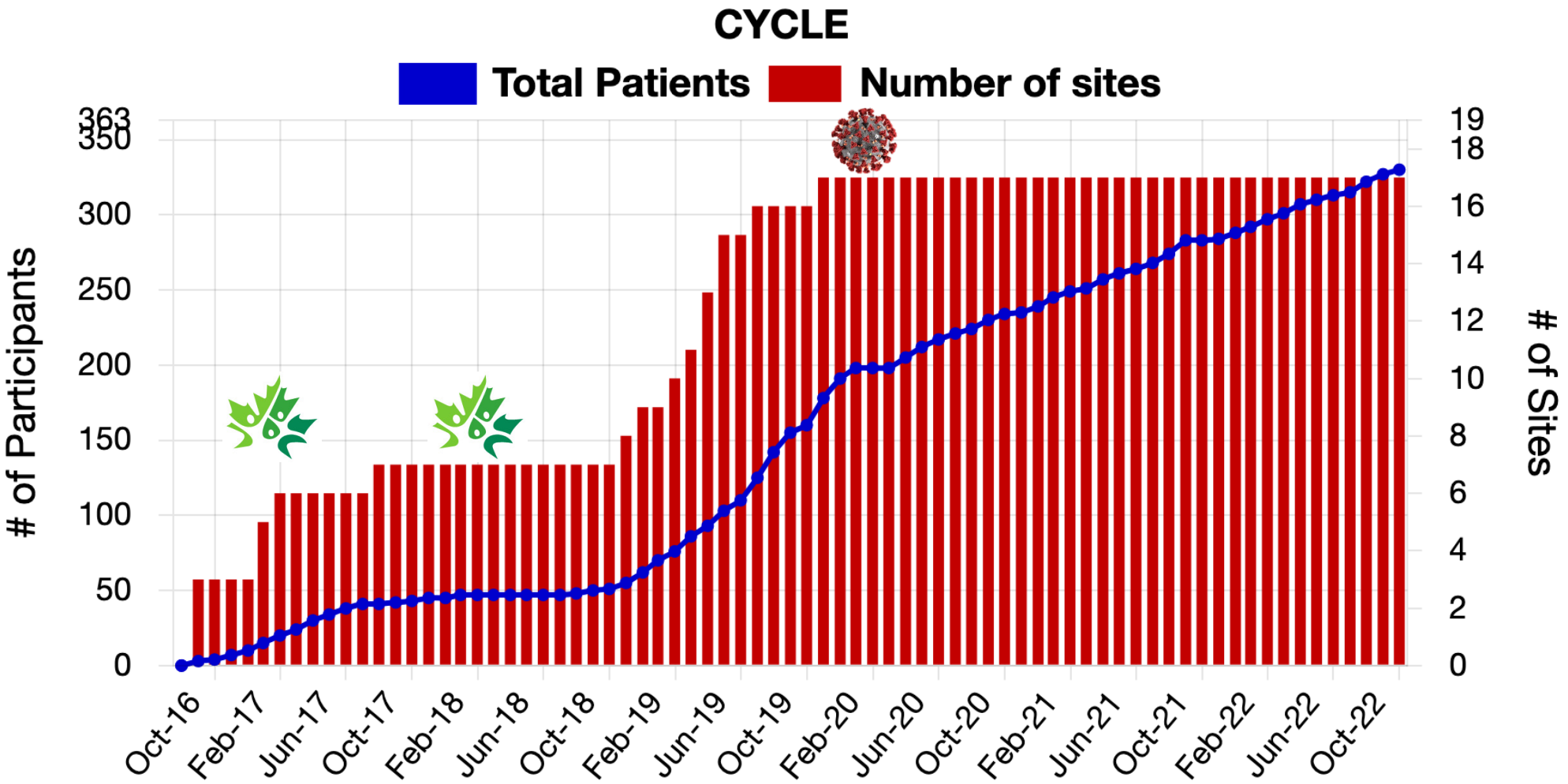
Clinicians as interventionists, outcomes assessors

Engagement & Training:

- >80 ICU PT interventionists
- >170 acute care outcome assessors
- >100 research personnel
- 18 centres, 3 countries
- Academic and community hospitals



CANADIAN CLINICAL RESEARCH NETWORK

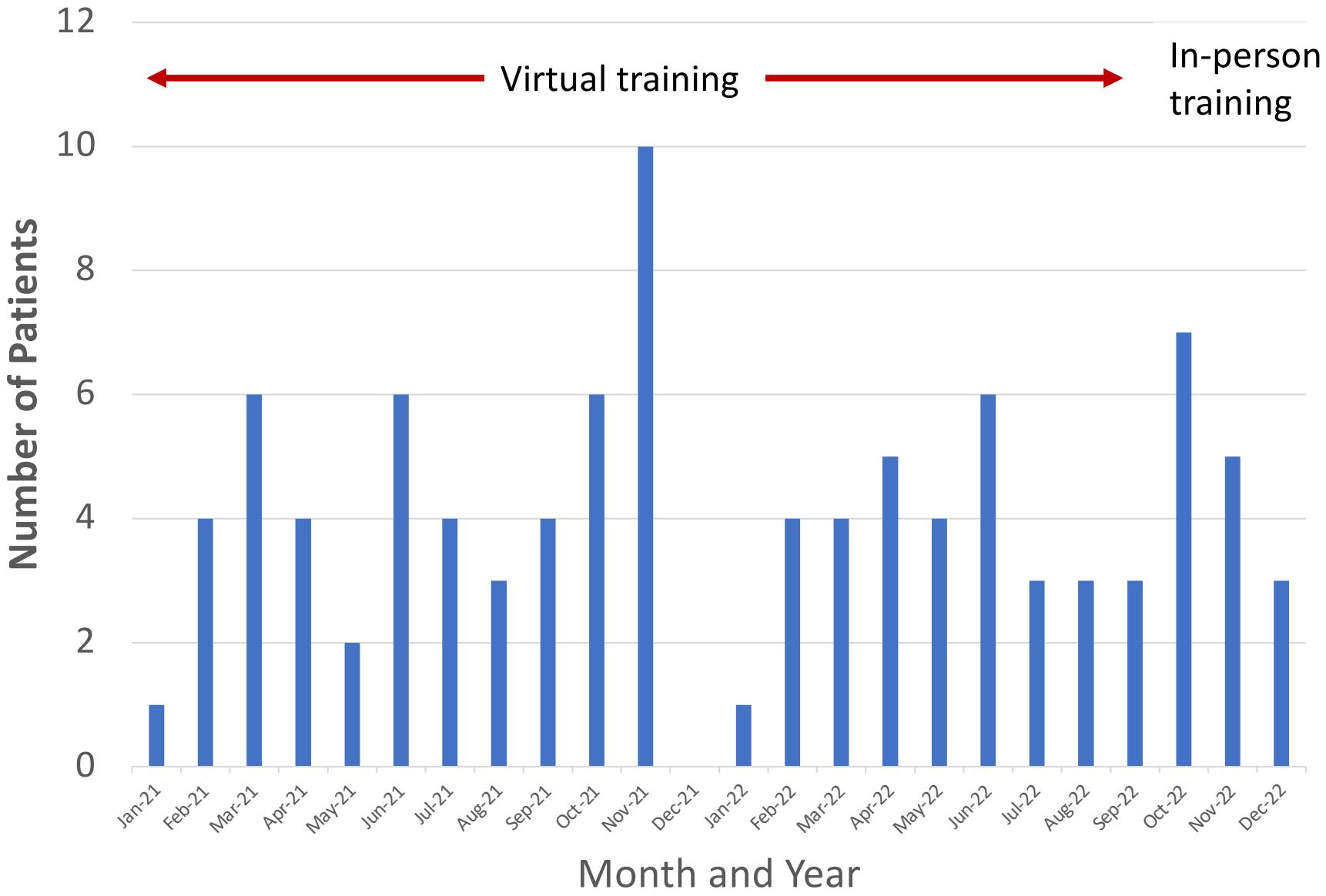


CYCLE Vanguard
NCT02377830
Oct 2016

CYCLE RCT
NCT03471247
Nov 2018

CYCLE Monthly Enrolment 2021-2022

Average: 4 pts/ month

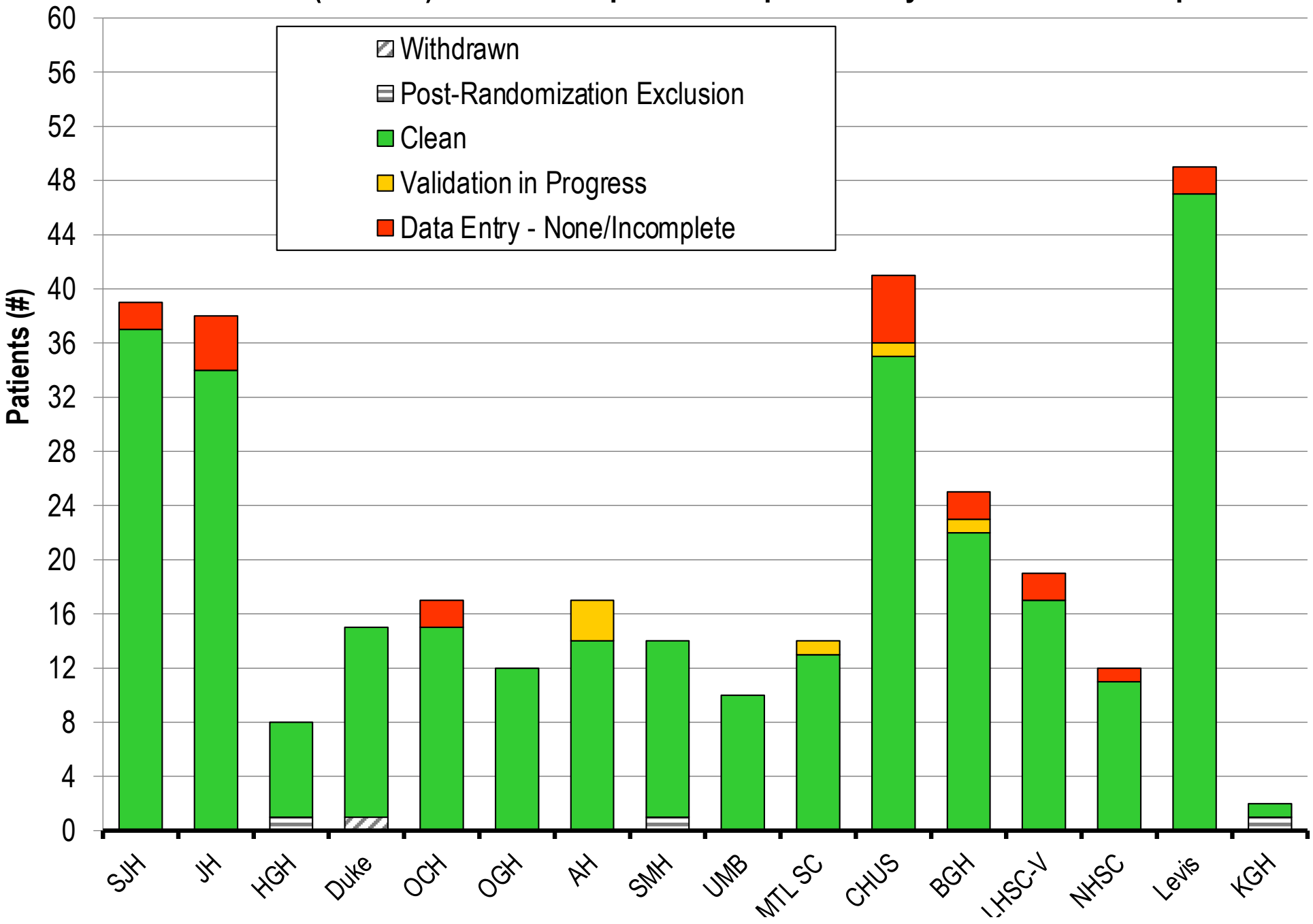


Enrolment by site - CYCLE RCT

Site	# Enrolled			
	Vanguard	RCT	Total	*Since Interim Analysis*
St. Joseph's, Hamilton	11	28	**39**	*13*
Juravinski, Hamilton	9	29	**38**	*14*
Hamilton General	3*	5	**8**	*0*
St. Michael's, Toronto	-	14	**14**	*1*
Duke, USA	-	9	**15**	*1*
Mount Sinai, Toronto	1	0	**0**	*0*
University of Maryland, USA	8	10	**10**	*1*
Ottawa Civic	9	16	**17**	*12*
Ottawa General	6	4	**12**	*1*
Austin Health, Australia	-	8	**17**	*6*
Montreal Sacre Coeur, Quebec	-	14	**14**	*8*
Sherbrooke, Quebec	-	41	**41**	*31*
Kingston General	-	2	**2**	*0*
Brantford General	-	25	**25**	*17*
London Victoria	-	19	**19**	*13*
Niagara Health, St. Catharines	-	12	**12**	*2*
Hotel Dieu de Levis, Quebec	-	49	**49**	*29*
OVERALL	**47**	**285**	**332 (92% total)**	*149*

Data as of December 12, 2022

DATA VALIDATION


Data Validation Status - CYCLE RCT
332 patients randomized data (as of Dec-12-22)
97.4% (306/314) validated of pts died or post 90 days and d/c from hospital
Withdrawn
Post-Randomization Exclusion
Clean
Validation in Progress
Data Entry - None/Incomplete
Patients (#)
60
56
52
48
44
40
36
32
28
24
20
16
12
8
4
0
SJH
JH
HGH
Duke
OCH
OGH
AH
SMH
UMB
MTL SC
CHUS
BGH
LHSC-V
NHSC
Levis
KGH

Case Report Form Validation by Site - CYCLE RCT

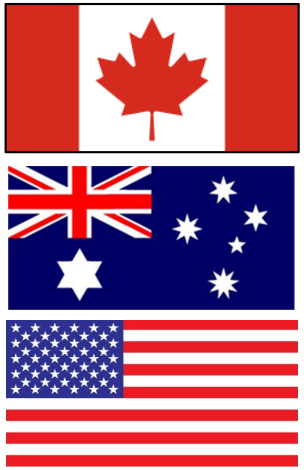
Site (#)	Pts. Rand. (#)	Total CRFs (#)	`Clean` CRFs (#)	Clean (%)
SJH (01)	38	3002	3000	99.9
JH (02)	38	2224	2204	99.2
HGH (03)	8	370	364	99.7
SMH (04)	14	1161	1156	100.0
Duke (05)	15	905	901	99.9
Sinai (06)	0	47	45	95.7
UMB (07)	10	745	739	100.0
OCH (08)	16	1303	1236	95.4
OGH (09)	12	351	326	92.9
AH (11)	17	556	535	96.2
MTL (16)	14	1081	1043	96.5
SHE (17)	39	2338	2303	98.7
KGH(29)	2	179	169	94.4
Brant (32)	24	2042	2002	98.9
LHSC (34)	17	1436	1331	93.4
NHSC (43)	11	903	873	97.3
HDL (50)	47	3354	3261	98.9
TOTAL	**322**	**21997**	**21488**	**98.2**

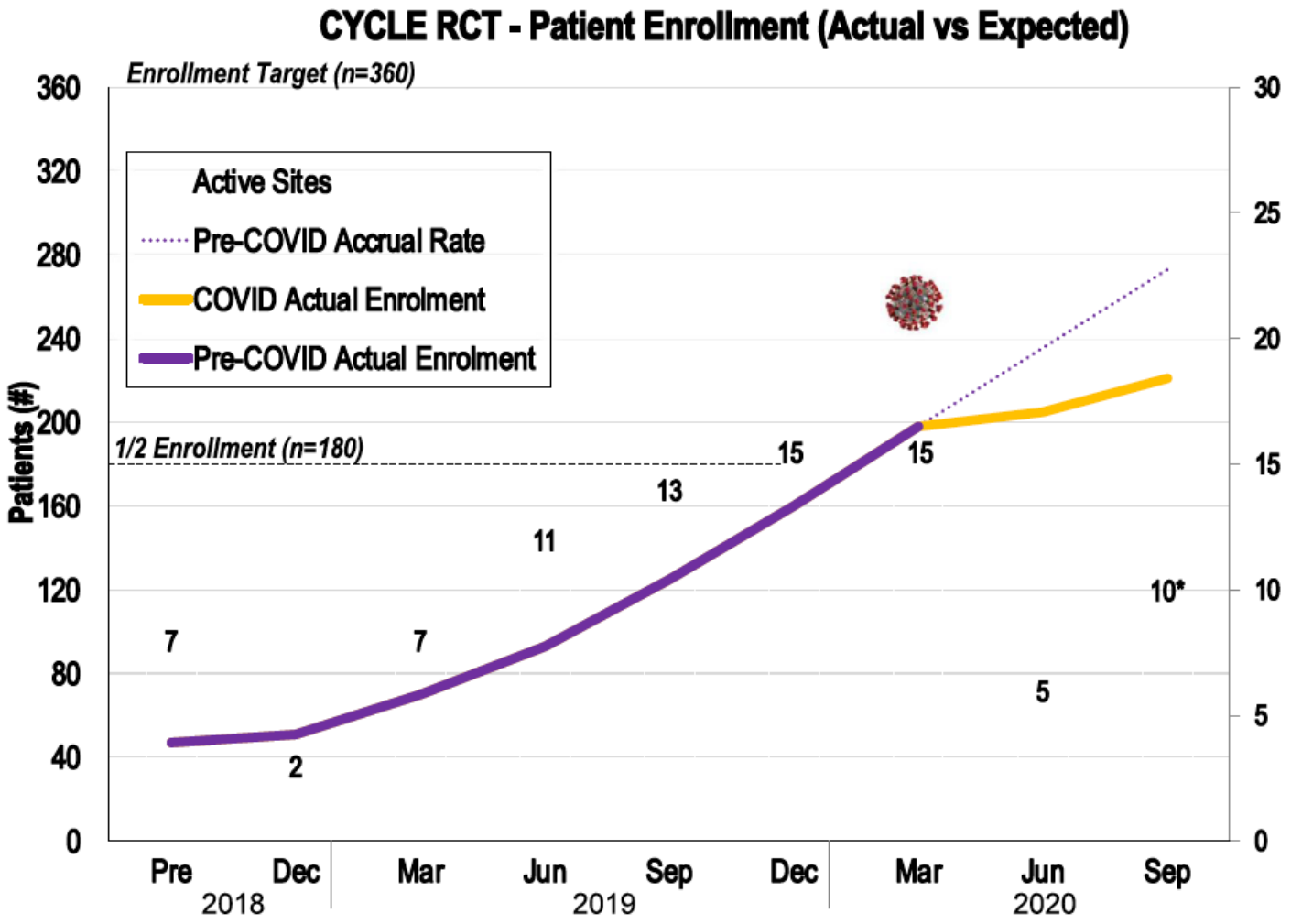
Data as of December 8, 2022

MANUSCRIPTS

Research interrupted: applying the CONSERVE 2021 Statement to a randomized trial of rehabilitation during critical illness affected by the COVID-19 pandemic

Julie C. Reid[1,2*], Alex Molloy[1], Geoff Strong[1,2], Laurel Kelly[1], Heather O'Grady[1,2], Deborah Cook[1,3,4], Patrick M. Archambault[5,6], Ian Ball[7], Sue Berney[8,9], Karen E. A. Burns[10,11], Frederick D'Aragon[12,13,14], Erick Duan[1,3,15], Shane W. English[16,17,18], François Lamontagne[12,14], Amy M. Pastva[19], Bram Rochwerg[3,4], Andrew J. E. Seely[17], Karim Serri[20], Jennifer L. Y. Tsang[3,15], Avelino C. Verceles[21,22], Brenda Reeve[23], Alison Fox-Robichaud[3], John Muscedere[24], Margaret Herridge[25], Lehana Thabane[4,26], Michelle E. Kho[1,2] and on behalf of the CYCLE Investigators





Manuscripts and Next steps

Manuscripts

- Protocol paper – pls submit feedback by Dec 15, 2022
- Statistical analysis plan paper in progress

Upcoming Safety Analysis – March 2023

Administrative

- Consent form updates to local REBs
- Contract extensions

SOP for secondary analyses

Complete enrolment – ideas to cross the finish line?