

PREFERRED

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Faculty/Presenter Disclosure

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Patients receiving hemodialysis are at high risk of fragility fracture

- Fragility fracture risk >5x greater than those without CKD
 - Greater length of hospital stay
 - 2x increase in in-hospital mortality
- Fracture prevention is difficult in hemodialysis
 - Patients excluded from research studies
 - Drugs can be contraindicated
 - Complex, mixed bone disease

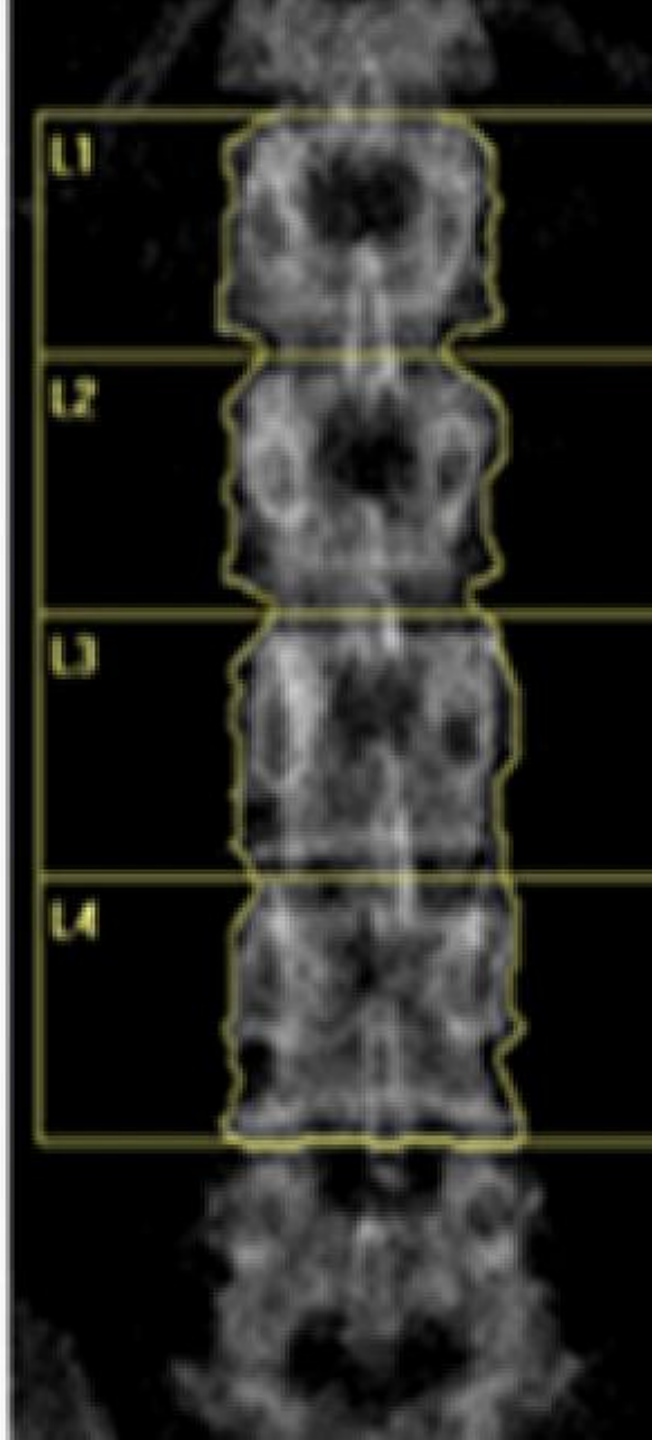
Fracture preventing therapies are available



- Highly effective medication approved by Health Canada for treatment of osteoporosis for over a decade
- Drug action and metabolism not dependent upon kidneys
- Can be prescribed to patients with CKD including dialysis

Studies of denosumab in ESKD have had methodological shortcomings

- Small observational studies without comparators
- Small explanatory RCTs focused upon BMD and bone turnover



Increased risk of hypocalcemia with denosumab use in routine care

- 0.6% vs. 0.3% of new users of denosumab vs. bisphosphonates experience corrected calcium <2.00 mmol/L within 180 days
- eGFR <15 ml/min/1.73m² or receiving maintenance dialysis, incidence is 24.1% (95% CI 18.1, 30.7)
 - 14.9% (95% CI 10.1, 20.7) for a calcium <1.80 mmol/L



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- Randomized controlled trial of denosumab in people using maintenance in-centre dialysis
- Pragmatic RCT
 - Does this intervention (vs. usual care) prevent fragility fracture in hemodialysis under usual conditions?
- Randomized 1:1 to intervention vs. usual care
- Intervention
 - In-unit administration of subcutaneous denosumab every 6 months
 - Early, protocol guided calcium and vitamin D prophylaxis
 - Close calcium monitoring



| | | | |
|------------------------------|---|---|---|
| Eligibility | Women aged 60-90 years, BMD -4.0 to -2.5, off osteoporosis therapies for at least 12 months | 40+ years, high risk of fracture, optimized CKD-MBD, no contraindications | 40+ years, high risk, optimized CKD-MBD, no contraindications |
| Recruitment | Research staff at participating site | Kidney care team | Health care provider |
| Setting | Participating site | Hemodialysis unit | Hospital/office |
| Organization | | | |
| -Pre-screen and screening | -Research staff | -Kidney care team | -Health care provider |
| -Consent | -Research staff | -E-consent by central RA | -Health care provider |
| -Documentation | -Research staff | -Kidney care team | -Health care provider |
| Flexibility | | | |
| -Intervention administration | -Research staff at study visit | -Kidney care team under flexible protocol | -Health care provider |
| Follow-up | Research staff at study visit | Hemodialysis ICES databases | Routine care follow-up |

Inclusion criteria

- Age ≥ 40 years
- Treating nephrologist/nurse practitioner in the dialysis unit deems that a prescription for study drug will be reasonable in the potential participant.
- Access to denosumab through provincial drug benefits (i.e. evidence of receiving outpatient prescription medications through the Ontario Drug Benefits Program, Ontario Disability Support Program)
- Baseline albumin-corrected serum calcium ≥ 2.15 mmol/L, PTH 15-60 pmol/L (or 2-9x the upper limit of normal for the local laboratory), alkaline phosphatase (ALP) ≥ 80 IU/L.
- High risk of fragility fracture defined by the World Health Organization's Fracture Risk Assessment Tool), OR b) a prior history of hip or vertebral fracture (where the later could have been asymptomatic and only observed radiographically), OR c) two or more fragility fractures of the humerus, wrist, and/or pelvis

Exclusion criteria

- Expected to recover kidney function, stop hemodialysis, pursue palliative care, or transfer to home or peritoneal dialysis within 12 months of randomization (as assessed by a health professional)
- On the deceased donor transplant list for more than 2 years
- Expected to receive a live kidney donation within 1 year
- Expected to start IV bisphosphonates (i.e. pamidronate or zoledronic acid)
- Current use of cinacalcet (Sensipar)
- Current use of another osteoporosis medication
- Of childbearing status
- History of femur fracture attributed to osteoporosis medication use (i.e. midshaft femoral fracture or atypical femoral fracture)
- Major dental surgery planned within the next 6 months (e.g. root canal)
- Known allergy or intolerance to denosumab
- Expected to receive a parathyroidectomy for hyperparathyroidism in the next 12 months

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Aims

- Prove that our streamlined methods of enrollment will facilitate patient recruitment across multiple centres in a timely way;
- Prove there is good adherence to the trial protocol in usual care;
- Confirm patients are adherent to treatment assignment (i.e. intervention group to denosumab, minimal cross-over to denosumab in non-use group);
- Confirm there are no 'signals' of unmanageable harm (i.e. hypocalcemia) that would prevent testing of this intervention on a larger scale

Primary feasibility outcomes



Recruitment of 60 patients across multiple hemodialysis centres within 6 months of site activation

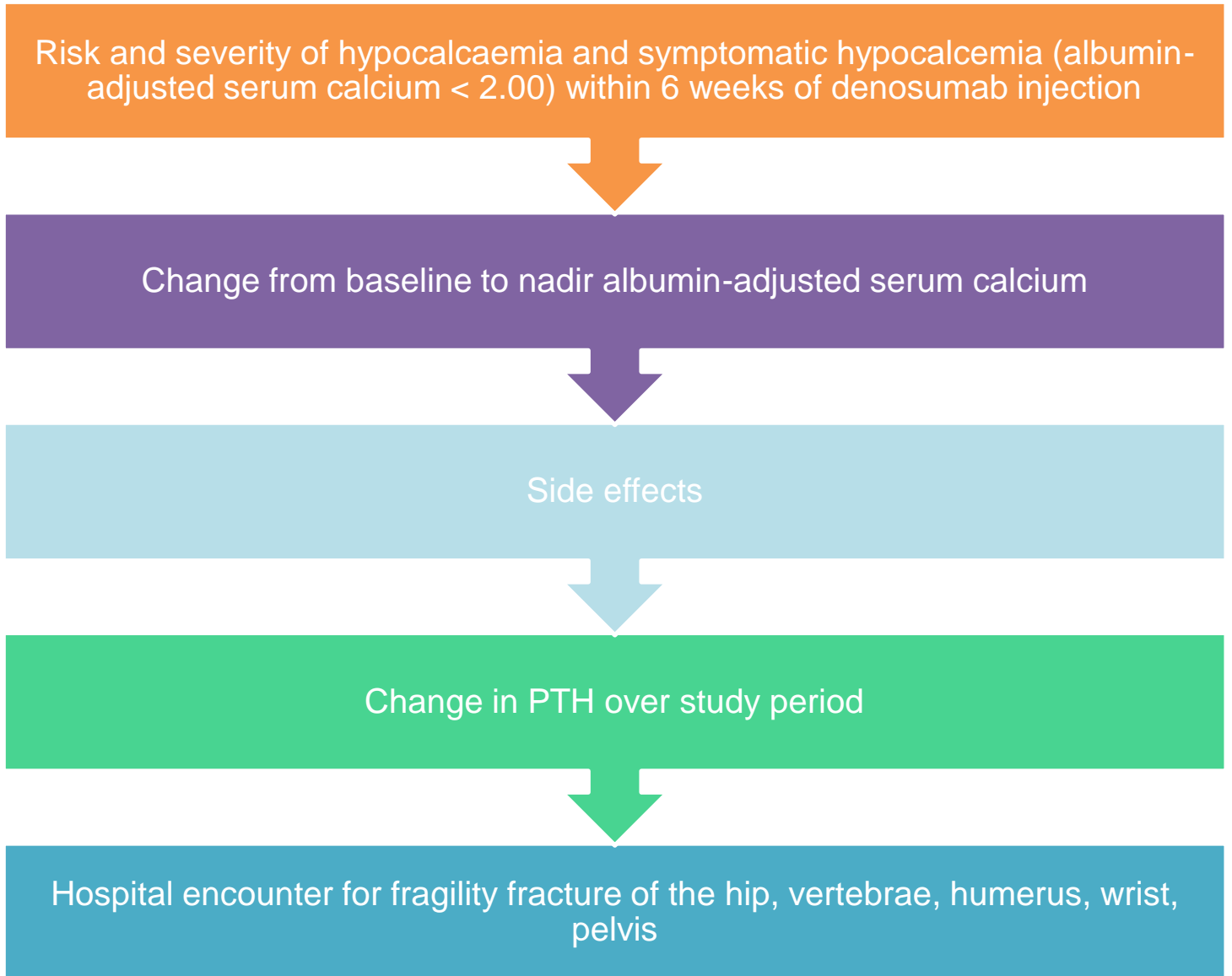


Participants randomly allocated to the intervention receive >90% of scheduled treatment at 0, 6, and 12 months



Participants randomly allocated to no denosumab (i.e. usual care) do not receive a prescription for denosumab over 15 months of follow-up

Secondary outcomes: Safety

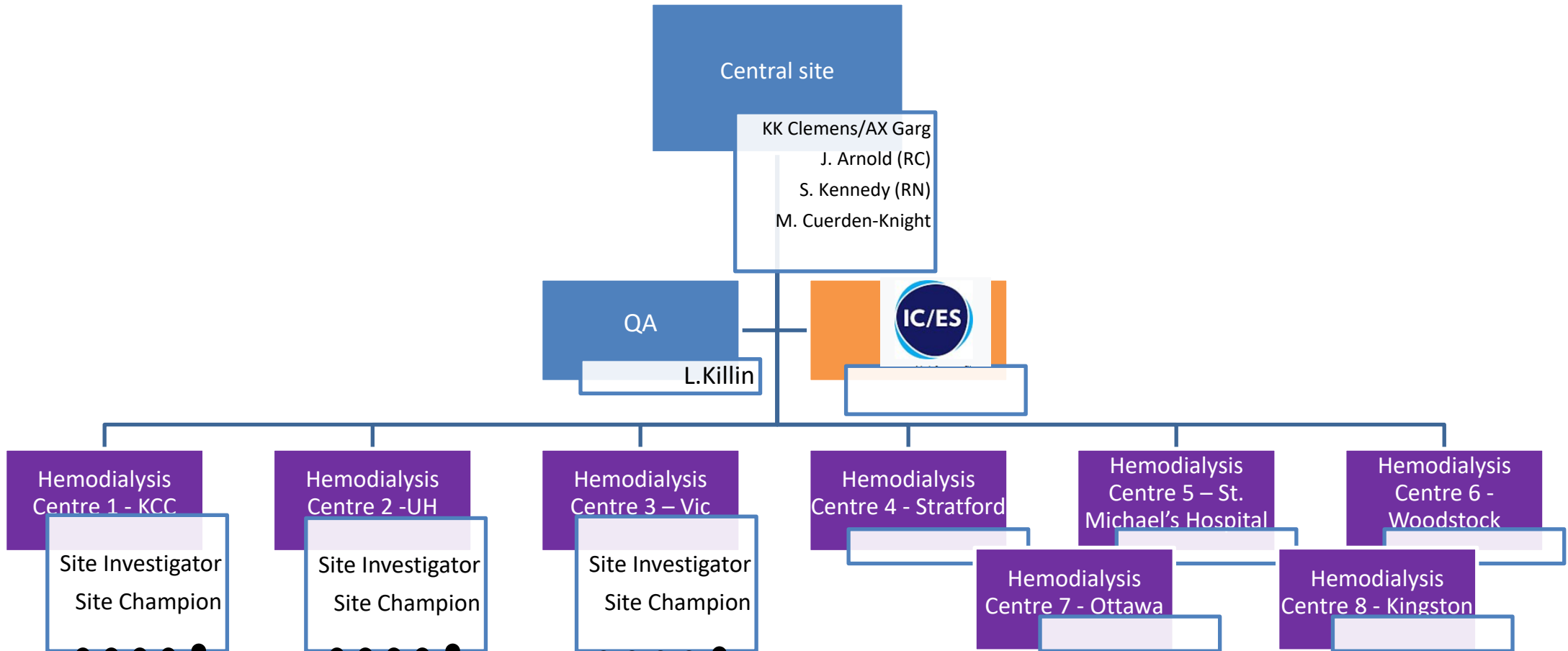


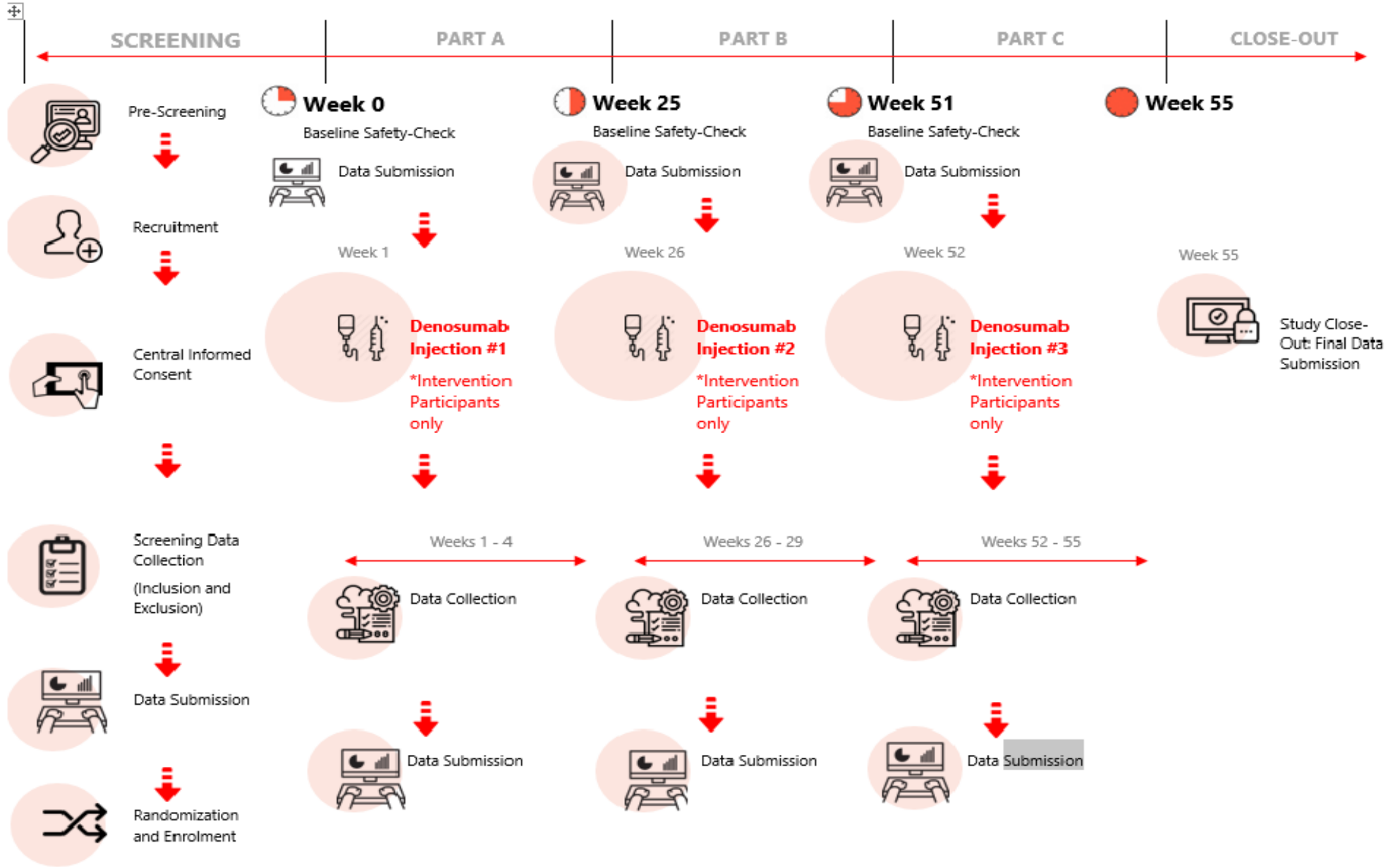
Secondary outcomes: Participant satisfaction

- Participant satisfaction with E-platform
- Participant satisfaction with study protocol

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DSMB





PREFERRED-1 Challenges



Pandemic

- Omicron wave
- Redeployment of staff
- Personnel turnover
- Institutional approval



Site

- Workload
- Summer holidays
- Prescreening and screening
- Amendment to facilitate RA support

London Health Sciences Centre

| Site | Activated | Recruitment Initiation |
|-------------|------------------|-----------------------------------|
| 1 | July 2022 | Oct 2022 |
| 2 | Nov 2022 | Dec 2022 |
| 3 | June 2022 | Sept 2022 |

Recruitment

105-179 available for prescreening across each LHSC site

10-20% eligible for PREFERRED-1

- 15-30% of those potentially eligible provide consent

Site activation planning Ottawa

Ethics approval Stratford

Ethics for St. Mike's, Queens, and Woodstock

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- 3-year rate of non-vertebral fracture 3.38 (3.13 - 3.65) to 9.14 (7.78 - 10.74) per 100 PY
- 5000 patients (253 events) for HR 0.7, power 80%
- Inclusion of research staff
- Recruitment of centres across Canada
- More funding
- Change to eligibility criteria?



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- Heather Lapier
- Lauren Killin
- Pragmatic Trials Team

Co-I and collaborators

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- Louise Moist

Site champions

- Julie Ann Lawrence
- Lindsay Blackwell
- Dennis Smith
- Barb Wilson
- Kerri Gallo
- Michelle Meijer

- Bonnie Field (PP)
- Matthew Weir
- Nabil Sultan
- Samuel Silver
- Amber Molnar
- Rachel Holden



| Fracture rate (placebo) | HR | Power | Number of events | Estimated sample size* | Estimated sample size** |
|--|------|-------|------------------|------------------------|-------------------------|
| 3.38 events per 100 PY | 0.85 | 80 | 1194 | 21,954 | 26,266 |
| 9.18 events per 100 PY with prior fracture | | 85 | 1366 | 25,116 | 30,046 |
| | | 90 | 1599 | 29,400 | 35,162 |
| | 0.8 | 80 | 636 | 12,020 | 14,366 |
| | | 85 | 728 | 13,758 | 16,434 |
| | | 90 | 852 | 16,100 | 19,232 |
| | 0.75 | 80 | 385 | 7484 | 8934 |
| | | 85 | 440 | 8552 | 10,220 |
| | | 90 | 515 | 10,010 | 11,960 |
| | 0.7 | 80 | 253 | 5064 | 6024 |
| | | 85 | 289 | 5784 | 6890 |
| | | 90 | 338 | 6764 | 8064 |