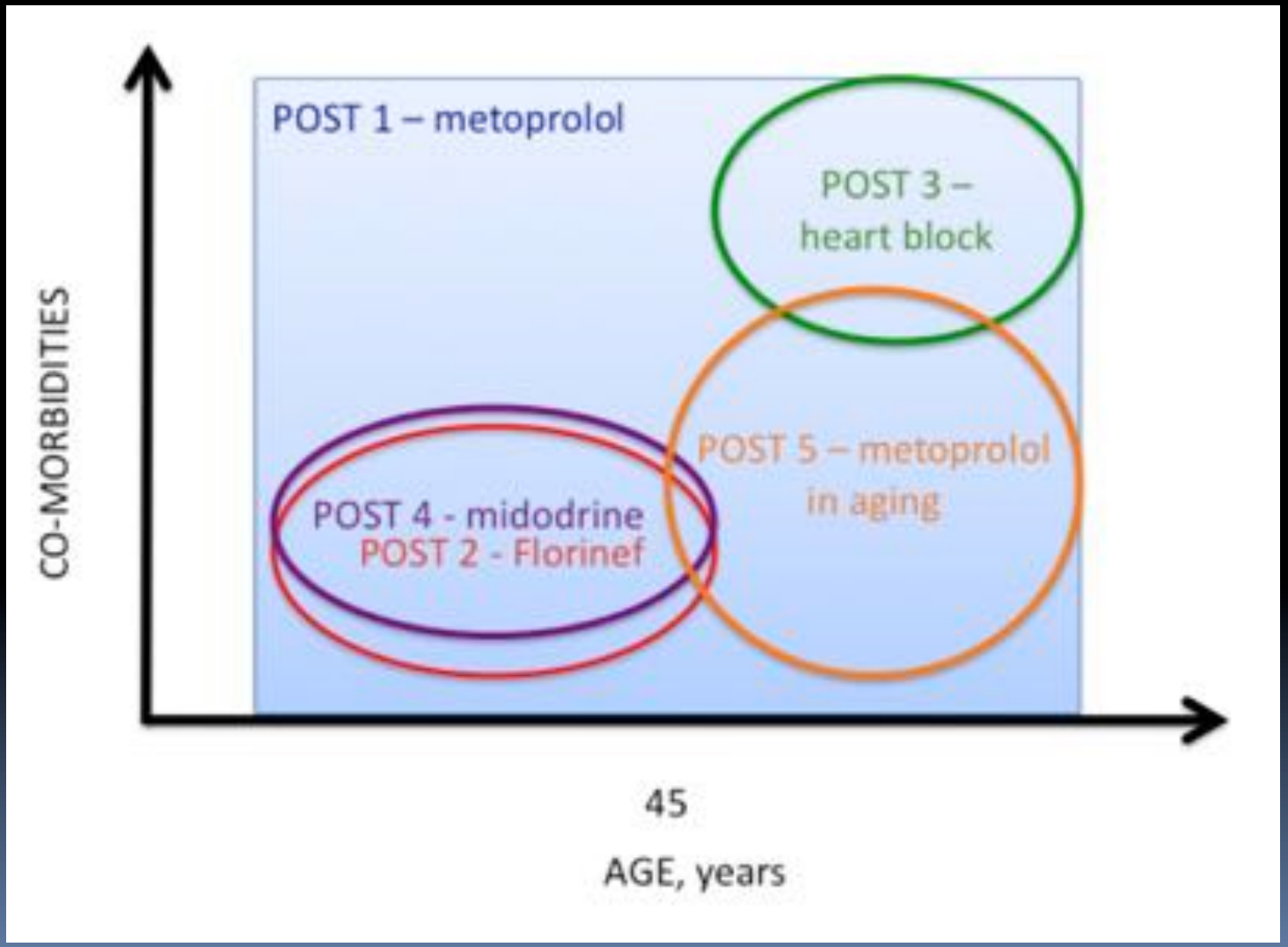
Venice 2015 Arrhythmias
Oct 17, 2015
Venice

PREVENTION OF SYNCOPE TRIALS

Agenda

1. Overview of POST programme
2. POST 3 status
3. POST 4 status & UK regulatory issues
4. POST 5 status & UK regulatory issues

PREVENTION OF SYNCOPE TRIALS LANDSCAPE



SPRITELY (POST 3)

***S*YNCOPE: *P*ACING OR *R*ECORDING IN *THE* *L*ATER *Y*EARS (SPRITELY)**

SPRITELY (POST 3)

SYNCOPE AND BIFASCICULAR BLOCK

- Most obvious cause: intermittent complete heart block
- Numerous competing co-morbidities: carotid sinus syncope, vasovagal syncope, IOH, orthostatic hypotension, sick sinus syndrome…
- What is the best approach?

SPRITELY (POST 3)

SYNCOPE AND BIFASCICULAR BLOCK

- Two competing strategies
- ILR: *primum non nocere*
- Pacemaker: *primum succerre*

SPRITELY (POST 3)

WHAT ARE THE RECOMMENDATIONS?

Pacemaker for syncope and bifascicular block: IIA

ILR for syncope and bifascicular block: IIA

SPRITELY (POST 3)

STUDY OBJECTIVE

- Syncope and bifascicular heart block:
- Does a *strategy* of empiric permanent pacing
- Provide *better overall combination* of suppression of syncope recurrences and device complications
- Than a *strategy* of acting on the results of an implantable loop recorder.

SPRITELY (POST 3)

STUDY DESIGN & FUNDING

- Randomized pragmatic, longitudinal, prospective, parallel design, open label, clinical trial
- Pacemaker versus ILR
- Funded by CIHR 2011-2016
- Three-year enrollment period
- Two-year fixed observation period

SPRITELY (POST 3)

INCLUSION CRITERIA

- ≥1 syncopal spell within 1 year preceding enrollment
- Bifascicular block on a 12-lead ECG
- Age ≥ 50 years
- Written informed consent

SPRITELY (POST 3)

EXCLUSION CRITERIA

- Previous ILR, pacemaker, ICD
- Class I indication for pacing
- LVEF <35%
- Contraindication to permanent pacing
- Hypertrophic cardiomyopathy
- Sustained VT: spontaneous or induced
- MI in <3 months
- Epilepsy with (+) EEG
- Definite documented other cause

SPRITELY (POST 3)

PATIENT POPULATION

- 120 randomized, 70% male
- Mean age: 77 years
- Mean faints prior year: 2
- Mean lifetime faints: 5

SPRITELY (POST 3)

OUTCOME EVENTS

- Primary outcome is a composite
- MASRE: **M**ajor **A**dverse **S**tudy-**R**elated **E**vents
  - Syncope
  - Symptomatic bradycardias
  - Asymptomatic bradycardias leading to intervention
  - Acute & chronic device complications
  - Cardiovascular death

SPRITELY (POST 3)

POWER

- 90% power to detect a reduction ($p<0.05$) in the primary outcome measure from 71% (loop recorder group) to 30% (pacemaker group)
- relative risk reduction of 58%.
- 120 subjects

SPRITELY (POST 3)

OBSERVATION PERIOD

- 2-year ~~fixed~~ *minimum* period
- Seen as usual in device clinics
- 0, 6, 12, 18, 24 months, then q6 months until end
- Patients contact clinics with problems or events
- Device replacement and cross-over at discretion of site, and reasons documented

SPRITELY (POST 3)

FINANCES

- 5-year grant from CIHR (Canadian Institutes of Health Research)
- 2011-2016 with probable unpaid extension
- About $132k or 80,000 UK pounds yearly

SPRITELY (POST 3)

UK STUDY CENTRES

- 25 centres in Canada, US, UK, Japan, Malaysia
- UK coordinating centre Kings College Hospital, London UK (Nick Gall and Jon Breeze)
- James Cook University Hospital, Middlesbrough (Nick Linker)
- Morriston Hospital, Swansea (Mark Anderson)

SPRITELY (POST 3)

STUDY ENROLMENT

Figure. Patient Enrollment status (as of May 20, 2015)

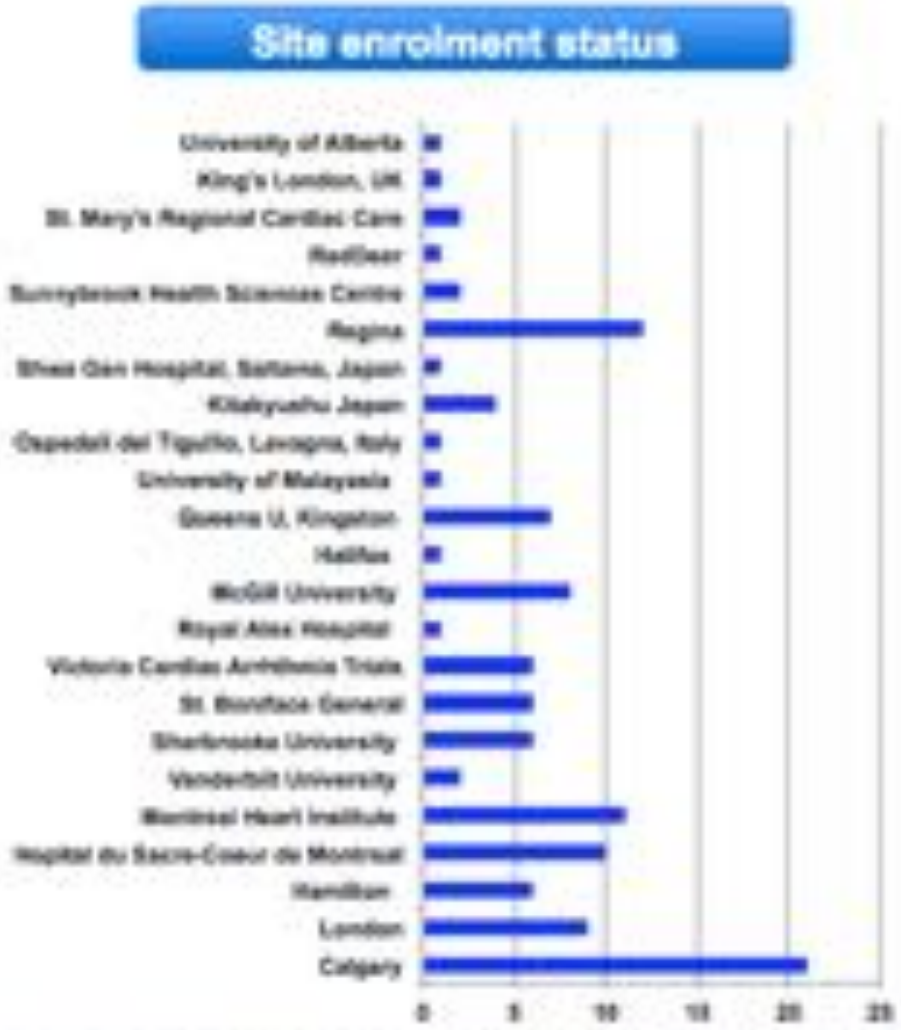


Figure. Centres in POST III and number of patients enrolled at each centre (As of May 20, 2015)

SPRITELY (POST 3)

COMPLETION TIMELINE

- May 20 2015: end of randomization
- May 20 2017: nominal end of data collection
  - Data cleansing already underway
  - Adjudication committee part done
- Summer 2017: results released
- Summer 2017-spring 2018: main publication

POST 4

ASSESSMENT OF MIDODRINE IN THE PREVENTION OF VASOVAGAL SYNCOPE (POST 4)

POST 4

MIDODRINE EFFECTS

- Prodrug for alpha$_1$ adrenergic agonist
- Does not penetrate blood brain barrier
- Metabolite half life 2.5 hours
- Increases venoconstriction and arteriolar constriction
- Increases preload and peripheral resistance

POST 4

MIDODRINE & VASOVAGAL SYNCOPE

- Five randomized trials
- None had the combination of all of:
  - ✓Randomized
  - ✓Double-blind
  - ✓Placebo-controlled
  - ✓Moderate severity adult population
  - ✓Adequately powered
  - ✓Clinical outcomes

SPRITELY (POST 3)

DATA COLLECTION

- Data Coordination Centre: University of Calgary
- RedCap on-line software
- Running very smoothly

POST 4

OUTCOME EVENTS

- Primary outcome is syncope
- Secondary outcomes
  - Quality of life (ISQL, EQ5D)
  - Presyncope number, severity, duration
  - Costs
  - Associated biomedical studies

POST 4

ENROLLMENT ASSUMPTIONS

- 20 centres
- Control syncope-free survival 45%
- Midodrine syncope-free survival 75%
- Sample of 102 pts gives 85% power, $p < 0.05$
- Inflate 25% for 20% drop-out to 128 subjects

POST 4

POST 4 CENTRE ENROLMENT

- 23 centres activated
- 1 Mexican & 5 UK centres underway
- Enrolling patients for 42 months

POST 4

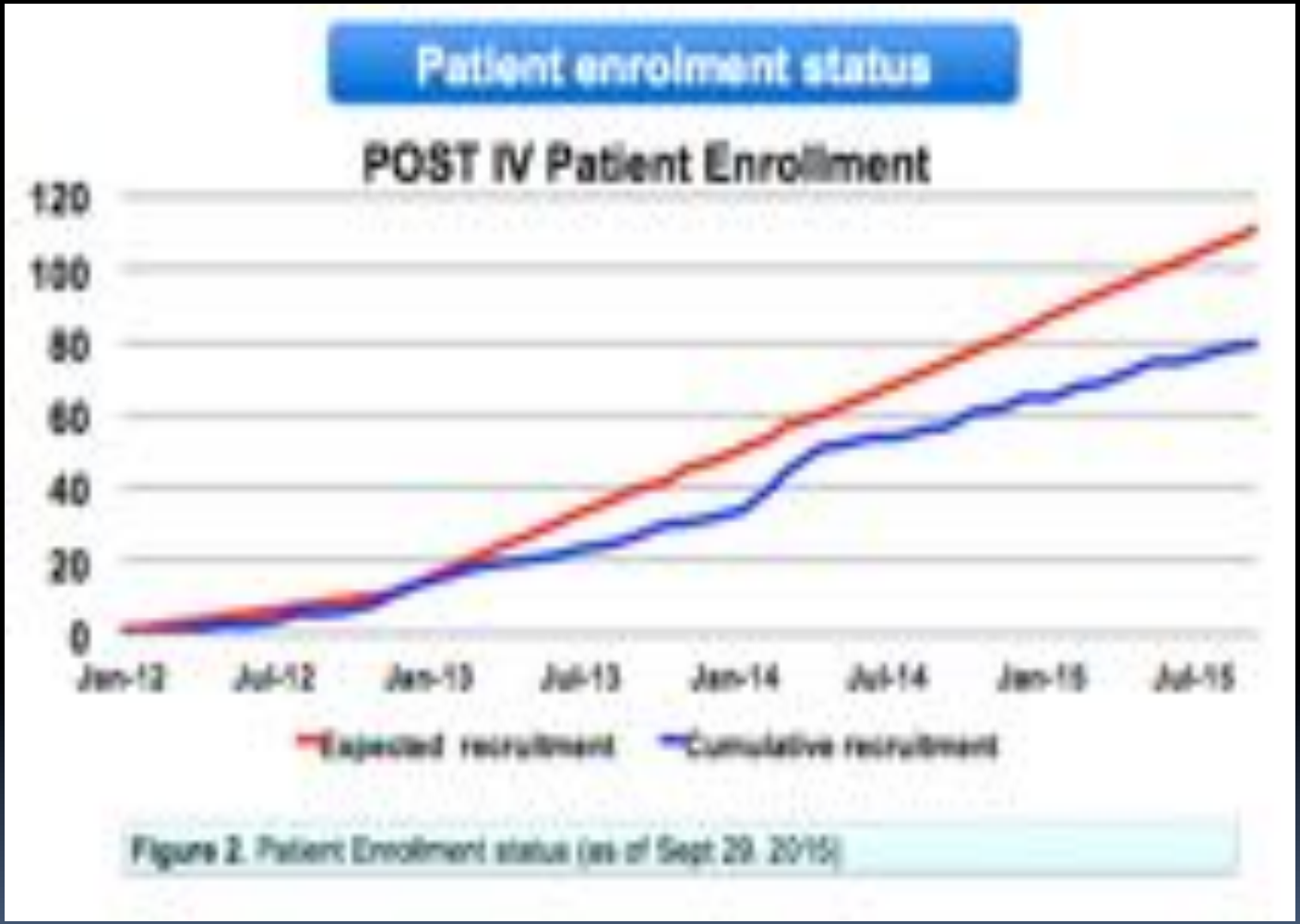


Figure 2. Patient Enrollment status (as of Sept 29, 2015)

POST 4

Figure 2. Centres in POST IV and number of patients enrolled at each centre (As of Sept 29, 2015)

POST 4

PATIENT PROFILE

- Randomized: 80
- Female: 67%
- Mean age: 36
- Lifetime faints: Median 20
- Prior year faints: Median 7
- *This is a very symptomatic population*

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POST 4

Figure 1. Shows 80 patients recruited. 48 Needed to reach target of 128

POST 4

COMPLETION TIMELINE

- Target population 128
- 80 randomized by Sept 30 2015
- Averaging 2 per month, tenuously
- End of recruitment October 2017
- End of follow-up October 2018

ASSESSMENT OF METOPROLOL IN THE PREVENTION OF VASOVAGAL SYNCOPE IN AGING PATIENTS (POST 5)

POST 5

BETA BLOCKERS AND SYNCOPE

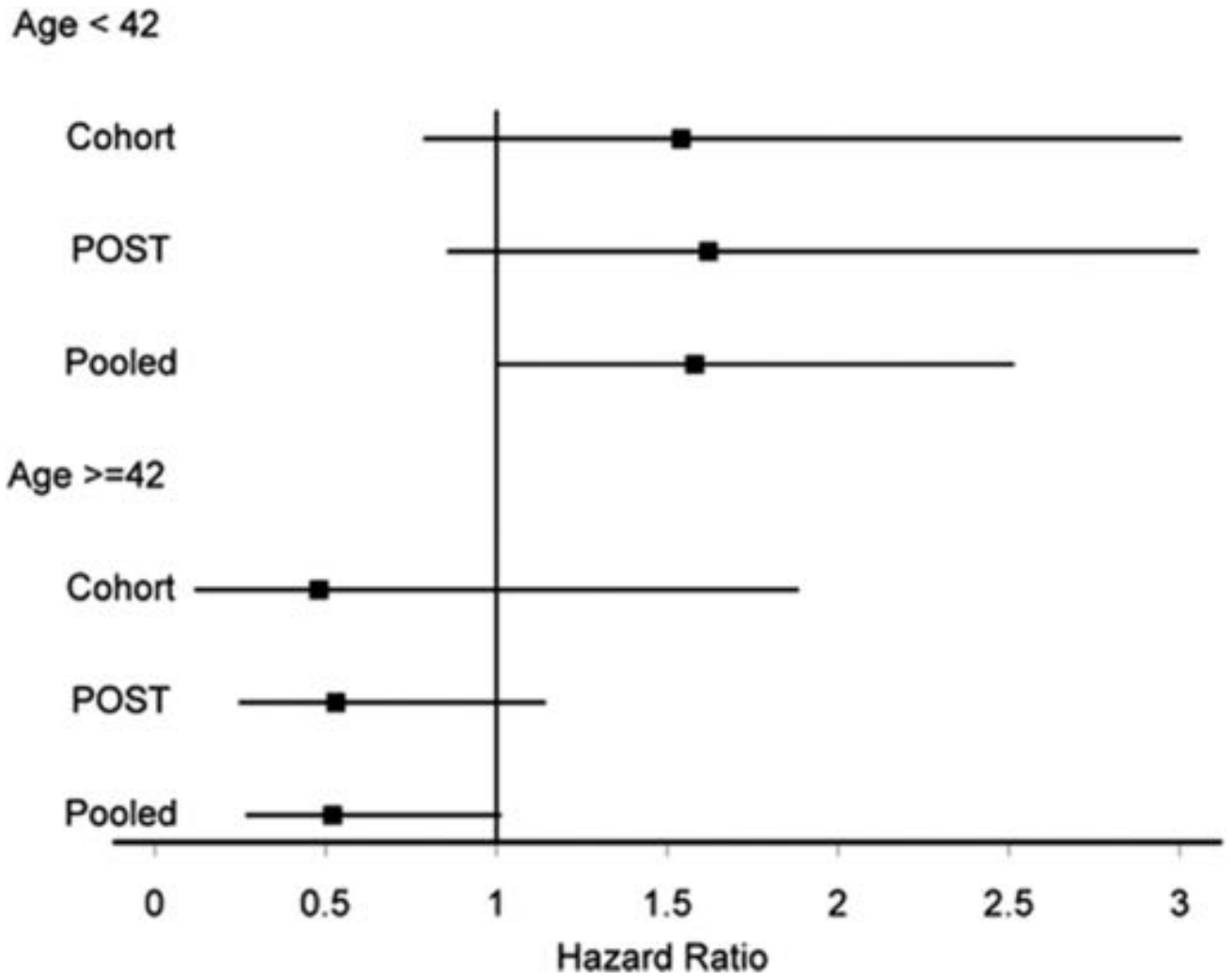
- Ample physiologic rationale
- Generally negative RCTs
- POST 1 was largest and pivotal RCT
- Included stratification on age 42 and prespecified age analysis

POST 5

BETA BLOCKERS, AGE, AND SYNCOPE

- Meta analysis of RCT and earlier observational study
- Asked whether beta blockers benefit patients >42.00 years old

Hazard ratios for a patient having a recurrence of syncope in both studies, for patients aged <42 years and ≥42 years.



Sheldon R S et al. Circ Arrhythm Electrophysiol 2012;5:920-926

POST 5

RCT of Metoprolol in older patients

- Randomized, prospective, placebo-controlled, parallel arm trial
- Metoprolol 25-100 mg bid
- Patients >40.00, >0 faints in previous year
- Diagnosis by Calgary Score
- Time to first syncope recurrence
- Intent to treat
- 5-year study with fixed 1-year observational period
- Secondary studies: frequency, QOL, cost

POST 5

RCT of Metoprolol in older patients

- 248 patients
- 85% chance at $p<0.05$ to detect 40% RRR
- Expected outcomes 50% on placebo, 30% treated
- Allows for 11% premature loss to follow-up

POST 5

DATA COLLECTION

- Data Coordination Centre: University of Calgary
- RedCap on-line software
- CRFs in RedCap drafted

POST 5

RCT of Metoprolol in older patients

- Funded by CIHR 2013-2018
- Mean $162k (~£100k) per year
- Approved by Health Canada, University of Calgary Ethics
- 35 have received full package
- Canada, US, Mexico, Columbia, UK, Brazil
- 6 sites activated
- First randomization Sept15 2014

POST 5

Figure. Patient Enrollment status (as of Sept 29, 2015)

POST 5

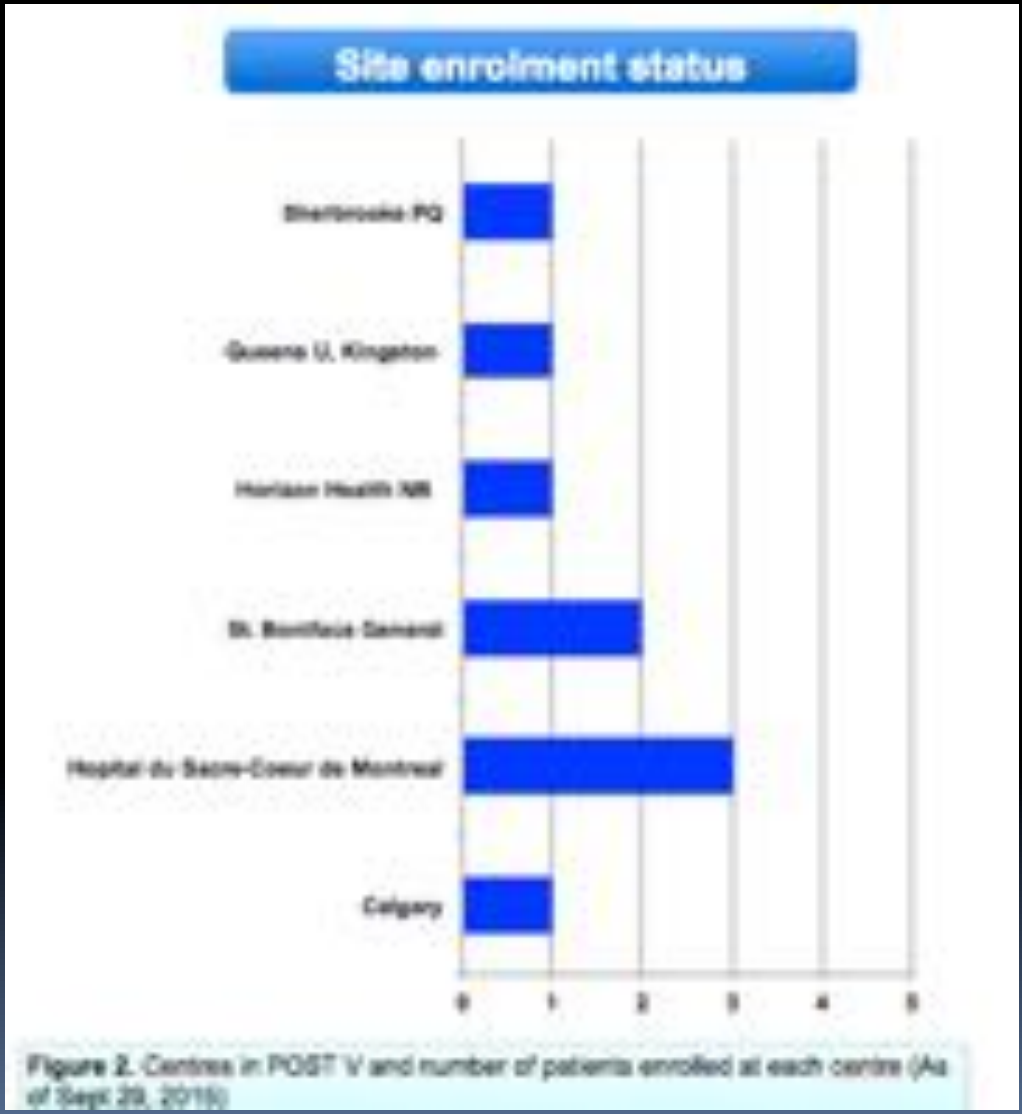


Figure 2. Centres in POST V and number of patients enrolled at each centre (As of Sept 29, 2015)