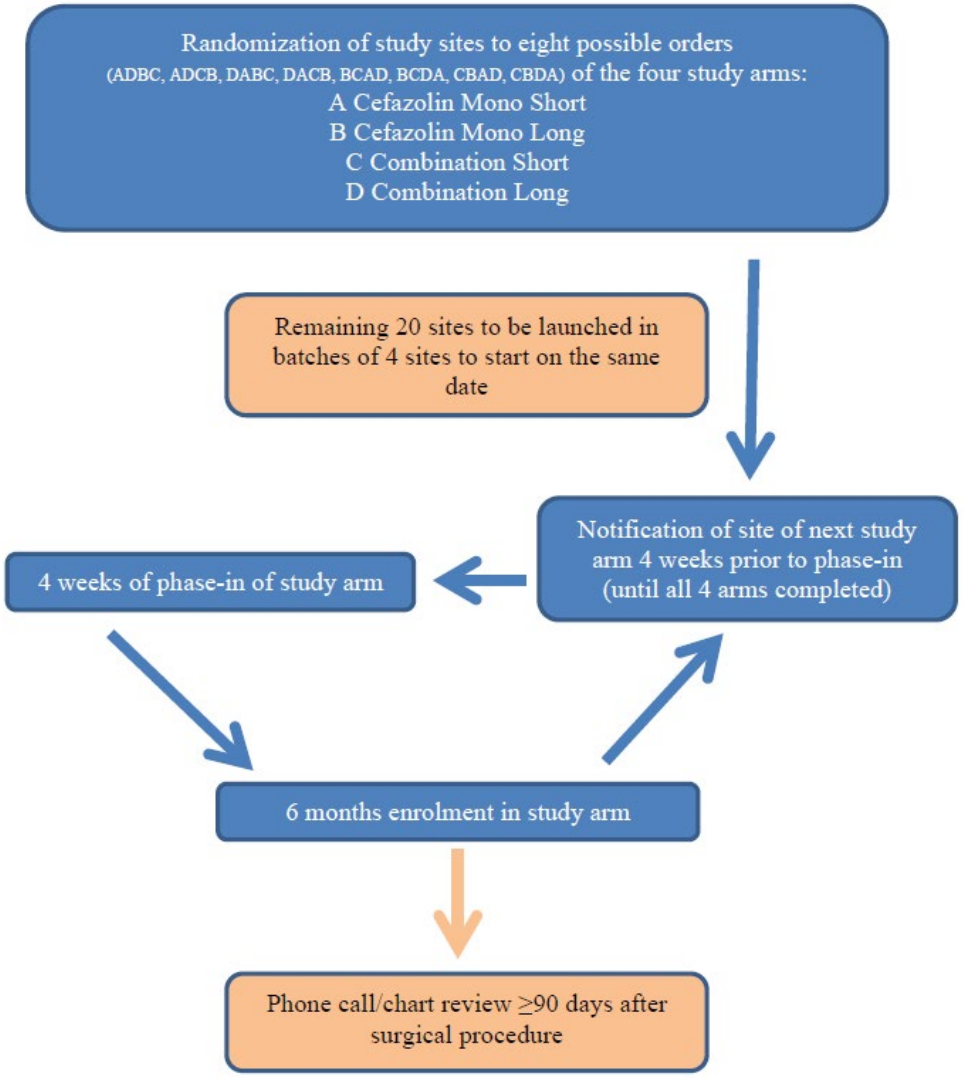
PICS PROTOCOL SYNOPSIS

TITLE OF STUDY	**P**revention of **I**nfections in **C**ardiac **S**urgery (PICS): a cluster-randomized factorial cross-over trial
FUNDING	CIHR
PRINCIPAL INVESTIGATOR	Dominik Mertz, MD, MSc
COORDINATING CENTER	Hamilton Health Sciences Corporation through its Population Health Research Institute (PHRI)
CLINICAL/REGULATORY PHASE	Phase IV
PARTICIPATING CENTRES	20 study sites in addition to 4 vanguard sites (~6000 participants) that already completed enrolment
STUDY OBJECTIVE	The primary goal is to determine the effects of dual antibiotic prophylaxis and of different durations of post-operative antibiotic prophylaxis on sternal surgical site infections in patients undergoing cardiac surgery.
STUDY DESIGN	Multi-center, factorial, cluster crossover study. Centers will be randomized to one of eight orders of the four study arms: a) cefazolin short-term, b) cefazolin long-term, c) cefazolin plus vancomycin short-term and d) cefazolin plus vancomycin long-term. Each study arm will be implemented for 6 months, and the strategy will become standard of care for all patients undergoing cardiac surgery during that time period. A wash-in period of one month prior to each arm will allow for the transition in management strategies.
NUMBER OF PARTICIPANTS	24 hospital sites with an average of 400 eligible participants undergoing cardiac surgery per strategy with 4 different strategies (4 periods; total of 38,400 participants)
STUDY DURATION	4 years. At the study site level, 4x6 months for the four study arms, 4x1 month for the phase-in, and 3 months follow-up after completion of study enrolment.
INCLUSION CRITERIA	≥18 years of age undergoing open-heart surgery (sternotomy, including minimally invasive sternotomies)
EXCLUSION CRITERIA	1. On systemic antibiotics or with an active bacterial infection at the time of surgery 2. Previously enrolled in this trial 3. Known to be colonized with MRSA 4. Beta-lactam or vancomycin allergy precluding the use of cefazolin or vancomycin, respectively 5. Participation in other studies that may interfere with this trial 6. Patients undergoing cardiac transplant
PARTICIPANTS INCLUDED IN ANALYSIS	All eligible patients during the study period.

PRIMARY OUTCOME	Composite outcome of any occurrence of deep incisional or organ/space (complex) sternal surgical site infections (s-SSI) following the CDC/NHSN definition[1] (Appendix B)
SECONDARY	1. All s-SSI including superficial incisional infections 2. Laboratory confirmed *C. difficile* infection 3. Mortality in participants with an active infection. 4. Acute kidney injury within 7 days of surgery[2] 5. Need for sternal revision surgery 6. Microbiology of s-SSI including relevant susceptibilities
INTERVENTIONS	*Cefazolin:* Cefazolin 2g (or 3g if greater than 120kg body weight) will be given within an hour of surgery. The intraoperative dose at 4 hours after the first dose or upon wound closure (whatever comes first) and the five post-operative doses in the long-term arms will be 2g every 8 hours. *Vancomycin:* Dosed at roughly 15mg/kg body weight intravenously, i.e. 1g or 1.5g if greater than 85kg body weight[3] and is to be administered within 60-90 minutes of the surgical procedure. The same dose will be used for the 3 post-operative doses in the long-term arm. Dosing will be adjusted in participants with renal impairment as per local standard practice.
RANDOMIZATION	Centers will be randomized to one of eight possible orders of the four study arms. Centers will get informed about the next study arm 4 weeks prior to the implementation of the following arm.
EVALUATION PERIOD	All outcomes will be evaluated 90 days after surgery as per the NHSN/CDC definition for s-SSIs.
ASSESSMENT OF EVENTS	The study sites will prepare case reports of all cases meeting criteria of a potential SSIs for the outcome adjudication committee. The reports will not include any information (e.g. dates) that would allow the blinded committee to guess the study arm of a particular participant.
STATISTICAL ANALYSIS	We will apply hierarchical modelling (generalized linear mixed model) for the primary analysis in order to adjust for cluster effects, stratified according to the factorial allocation in the intention-to-treat population meeting inclusion criteria.
DATA SAFETY AND MONITORING BOARD	An independent data safety and monitoring board will evaluate safety.
ADJUDICATION COMMITTEE	Blinded adjudication of the s-SSIs will be performed by a committee consisting of three members.


Randomization of study sites to eight possible orders
(ADBC, ADCB, DABC, DACB, BCAD, BCDA, CBAD, CBDA) of the four study arms:
A Cefazolin Mono Short
B Cefazolin Mono Long
C Combination Short
D Combination Long
Remaining 20 sites to be launched in batches of 4 sites to start on the same date
Notification of site of next study arm 4 weeks prior to phase-in (until all 4 arms completed)
4 weeks of phase-in of study arm
6 months enrolment in study arm
Phone call/chart review ≥90 days after surgical procedure