Challenges of emulating a target trial for surgical management of full-skin thickness pressure ulcers using routine data

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Introduction

Emulating a "target trial" requires the design principles from randomised controlled trials (RCTs) to be applied to analyses of non-randomised data for the same "PICO" research question [*Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. American Journal of Epidemiology. 2016;183(8):758-64*]. We emulated a target trial using routinely-collected health data to quantify the effectiveness of surgical reconstruction (SR) as treatment for a full-skin thickness pressure ulcer (SPU) (ISRCTN13292620).

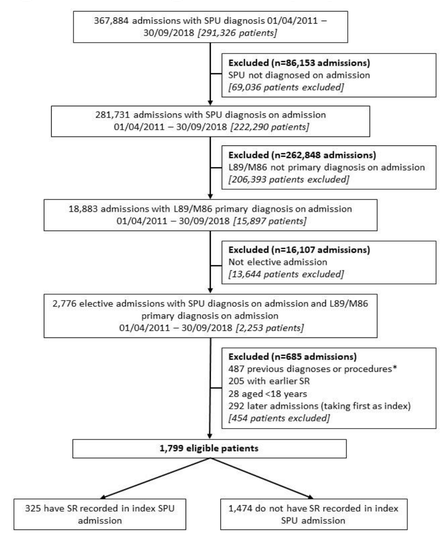
Methods

We obtained anonymised linked data from Hospital Episode Statistics and Office for National Statistics, describing 291,326 patients with a diagnosis of SPU (ICD-10 codes L89.2, L89.3, L89.9 or L89.X) between 01/04/2011 and 30/09/2018. We defined eligibility criteria, assignment to interventions (SR+ vs SR-) and start and end of follow-up by applying the target trial **PICO** (**P**opulation=patients with SPU as primary diagnosis on admission; **I**ntervention=SR [OPCS codes S17, S18, S19, S20, S22, S24, S25, S26. S27]; **C**omparison=non-surgical management; **O**utcomes=readmission with SPU diagnosed on admission [primary outcome, within one year of index admission], mortality [one of the secondary outcomes, within six months of index admission]) to our linked data.

Statistical methods

Analyses estimated the intention-to-treat effect of SRs. All factors identified as potentially related to the primary outcome of repeat admission with diagnosis of SPU were included in a backward stepwise logistic regression model to estimate propensity scores (PS). Significance for removing variables from the model was 0.25. Criteria for excluding tails of the PS distribution were chosen on the basis of non-overlapping regions of PS for SR+ and SR- groups. Kaplan–Meier curves were generated after adjusting by the inverse probability of treatment weights using the propensity scores, where the weights were defined as 1/propensity score for the treatment received.

Figure 1: Target trial population



L89 Decubitus ulcer and pressure area; M86 Osteomyelitis
**Previous diagnoses or procedures: dialysis, secondary cancer or heart failure in previous year, gangrene in previous three months*

Figure 2: SPU readmission (primary outcome)

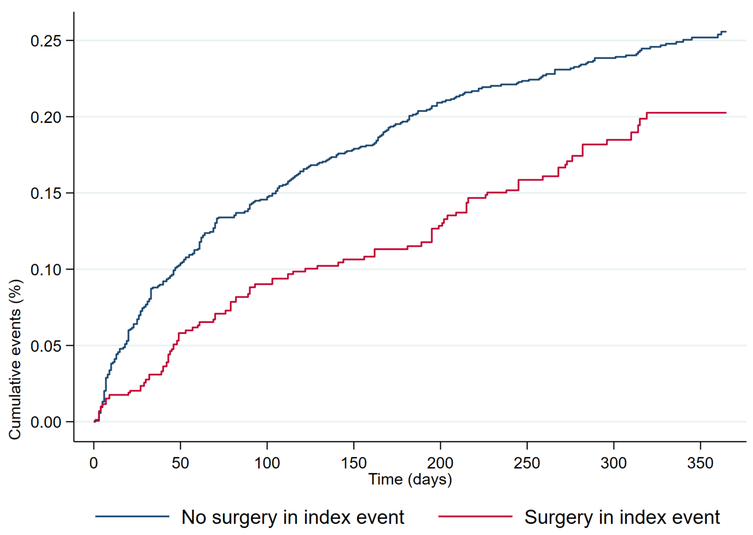
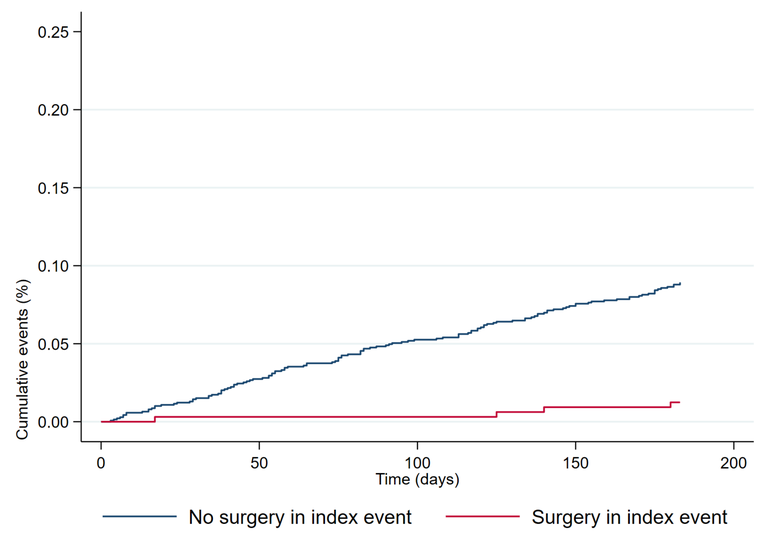


Figure 3: mortality (secondary outcome)



Results

- The large sample size reduced markedly by applying assumptions about the care pathway: SPU should be diagnosed ***on admission***, be the ***primary*** diagnosis, ***elective*** admission, and ***excluding patients with comorbidities*** that were considered likely to rule out SR (**Figure 1**).
- Patients in the SR+ group were younger than those in the SR- group, had fewer comorbidities (e.g. diabetes, hypertension, atrial fibrillation, cancer, kidney or liver disease) and more likely to have evidence of neurogenerative disease.
- Cox regression models estimated the hazard of readmission with SPU diagnosed on admission (**Figure 2**): after adjustment for age, sex, number of previous admissions, number of previous SPU admissions, various comorbidities and PS; HR 0.79, 95% CI (0.61, 1.03), p=0.07.

Challenges

We encountered two specific challenges in this target trial emulation:

- The comparator group may not be representative of the population eligible for the target trial since we had no information about patients who had a SPU but who did not have a hospital admission;
- Relevant outcomes such as wound healing time could not be defined from the dataset.

Our experience highlights the critical importance of understanding patients' care pathways at an early stage. Similarly, because most current interventions are delivered in the community, we did not reflect on outcomes that would likely be measured in the target trial (e.g. time to wound healing) and their availability in the routine data, or the importance of quality-of-life when surgeons and patients make decisions to offer SR.

Discussion

We planned the emulation when applying for funding without sufficiently detailed discussions with care teams, who were not familiar with the proposed method. We conclude that other researchers planning emulations, especially for non-pharmaceutical interventions, should ensure that these aspects are considered in detail.

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