RWD129

Feasibility of Target Trial Emulation (TTE) study design using the Hospital Episode Statistics (HES) database in England

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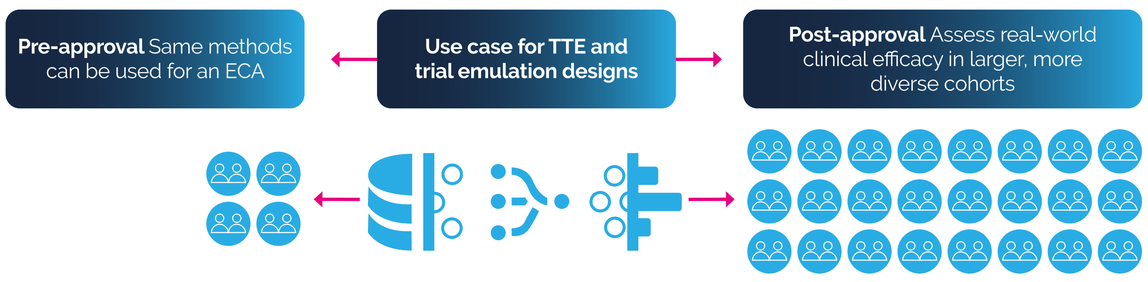
INTRODUCTION

- Target trial emulation (TTE) is a novel method whereby the principles of randomized controlled trials (RCT) are applied to observational studies.[1] This hypothetical emulation of RCTs can mitigate common sources of bias and confounding associated with observational studies.[2]
- Appropriate databases can be used for TTE, such as the Hospital Episode Statistics (HES) database, which records surgical interventions at procedure level for all operations across hospitals in England. This provides a source of high-quality real-world data (RWD) with a high population coverage.[3]
- The HES database can also be linked with other databases in England such as the Diagnostic Imaging Dataset (DID) and the Office for National Statistics Mortality Records (ONS) to provide a broad and informative real-world clinical dataset that can be utilised for trial emulation.
- Many regulatory authorities (including NICE [UK], HAS [France] and the EMA) propose TTE as an ideal approach for real-world evidence (RWE) study design. Hence, demonstration of TTE feasibility and its possible 'use case' in RWE studies (**Figure 1**) is warranted to inform future studies.

Figure 1. Use case for TTE and trial-emulation designs



OBJECTIVES

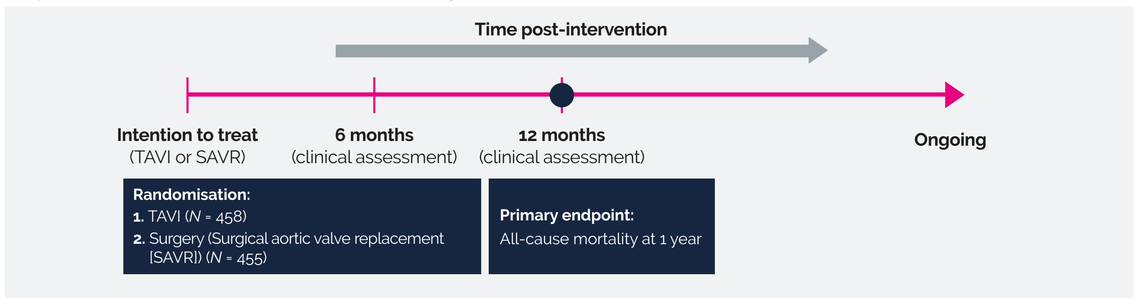
- The overarching objective of this project was to assess the feasibility of applying a TTE design to an RWE study using the HES database based on a previously published large UK-focused clinical trial.

METHODS

Target Trial

- The UK transcatheter aortic valve implantation (UK-TAVI) pragmatic trial was chosen based on a targeted literature review and initial feasibility assessment using data within HES. Study details are summarised in **Figure 2**.

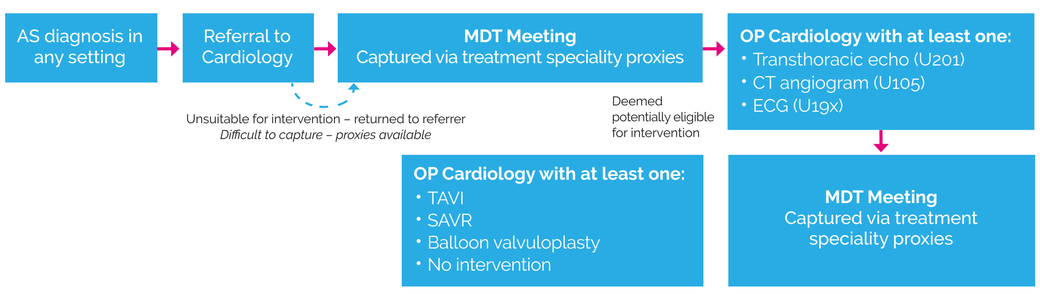
Figure 2. UK TAVI Trial Summary



Emulation of eligibility criteria within HES data

- Our aligning target trial design included an emulation of the intention-to-treat decision was developed around the HES database[3], shown in **Figure 3** and prevents temporal leakage of using future information to inform the past.

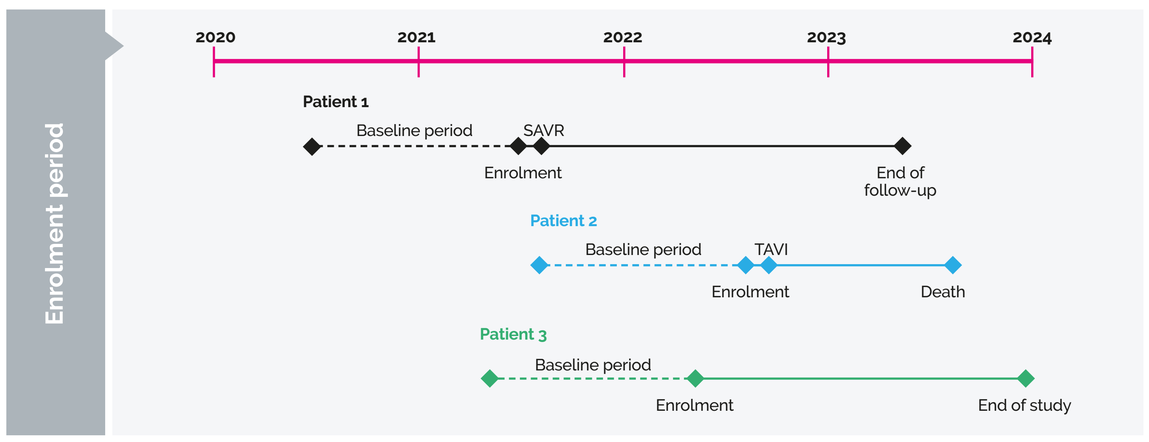
Figure 3. Determination of the intention to treat in HES data



Emulation of study time periods

- The availability of HES data dictate the possible study time periods for a TTE study and limits the ability to determine study outcomes.
- Key study time periods for the TAVI study are shown in Figure 4, with assignment to the SAVR control arm (Patient 1, black line) and the TAVR comparator cohort (Patient 2, blue line) per UK TAVI protocol.

Figure 4. Index dates, treatment assignment and follow-up



METHOD (CONT)

- Patient 3 (green line) is included within a "non-surgical intervention" cohort - meeting all eligibility criteria that can be defined within HES data, but who may not have been suitable. Within a perfectly emulated trial design Patient 3 is not plausible due to non-compliance to the protocol and thus represent an area where data acquisition through chart review or electronic health record extraction could provide tangible value.
- However, for the purposes of the HES TTE-TAVI design, the number of patients that do fall within this group can be used as a proxy for how well the UK TAVI eligibility criteria have been emulated.

Application To HES data

Whilst the primary endpoint of the TAVI trial is achievable using HES-DID-ONS data, not all secondary endpoints from the trial can be matched. Examples of this are summarised in **Table 1.**

Table 1. Endpoint Emulation Potential

ENDPOINTS	INCLUDED IN TAVI TRIAL?	CAN BE EMULATED FROM HES-DID-ONS DATA?
Primary endpoint:		
All-cause mortality at 1-year post-procedure	✓	✓
Secondary endpoints (5 examples):		
All-cause mortality at 30 days, 2, 3, 4 and 5 years	✓	✓
Re-intervention at 30 days and annually to 5 years	✓	✓
Death from any cause or stroke at 30 days and annually to 5 years	✓	✓
Quality of life (QoL)	✓	✗
Symptoms and functional capacity	✓	**Limited/requires proxies**

Statistical analysis

- The analytical methods of an RWE-TTE should be as practicably identical to those used in the target trial, with adaptations to a causal inference framework.
- As target-trial randomisation is not guaranteed in observational data, methods based on propensity scores will be used to control for confounding and selection biases.
- The final outcomes that estimate the intervention effect will therefore use these weightings and robustly estimated variances.

Biases, pitfalls & mitigation

Immortal time bias:
During the observation period, intervals where the outcome event cannot occur may be present. Appropriate study design will mitigate this source of bias.

Confounding bias:
Propensity score and IPW/OW statistical methods will mitigate confounding bias.

Temporal leakage:
While data already exist about the future outcomes of the patient, using this information results in emulation failure. Our TTE design accounts for this, including estimating intention to treat.

CONCLUSIONS

- **The results of this study indicate that it is likely that a robust, modern TTE design can be achieved using HES for some interventions, with careful consideration and a thorough understanding of the data itself.**
- The coverage and quality of the HES data would enable generation of high standard comparative RWE for HTA of surgical interventions and devices.
- Secondary datasets such as HES are able to provide compelling evidence in surgical interventions and medical devices, where RWE is typically less well established than with medicines
- Our research indicates secondary datasets such as HES are able to provide compelling evidence when combined with expert subject matter knowledge and study design.

REFERENCES

1. Matthews et al. *BMJ*. 2022 Aug 30;378:e071108

2. Hernán et al. *J Clin Epidemiol*. 2016 Nov;79:70-75

3. Zang et al. 2023 *Nature Communications* https://www.nature.com/articles/s41467-023-43929-1

DISCLOSURES

The authors are employees of OPEN Health.

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