Target Trial Emulation (TTE) for real world data analyses to support HTA decisions

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Background

Low risk Myelodysplastic syndrome (LR-MDS) is a chronic bone marrow malignancy most prevalent in the elderly, with an average age at diagnosis of 75 years.

The prognosis of patients with LR-MDS varies considerably and it is mostly affected by the lower than normal number of blood cells.[1]

Red blood cell transfusions can alleviate the anaemia symptoms but are expensive and carry risks for the patient experiencing iron-related toxicity.

The evidence base is growing regarding Erythropoietic Stimulating Agents (ESA) being able to mitigate the consequences of anaemia and that with early adoption can possibly delay the need for red blood cell transfusion. [2-5]

The evidence base regarding the effectiveness of ESA in an everyday clinical setting and particularly in an elderly population is scarce.[4]

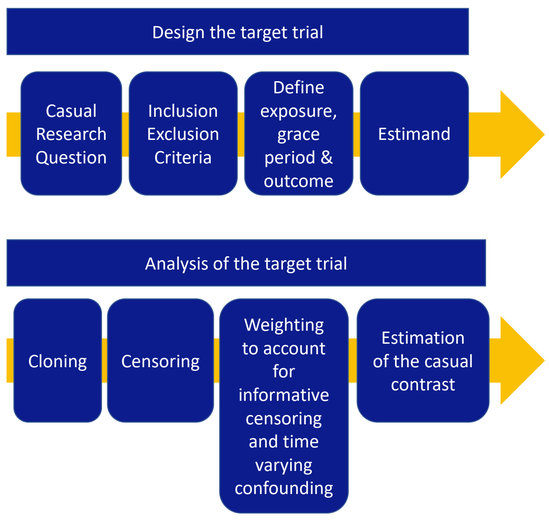
We use real world data (EU Myelodysplastic Syndrome (EUMDS) registry) to assess the impact of early initiation of first-line ESAs on the overall survival (OS) of LR-MDS patients versus a management strategy that does not involve ESAs

Methods

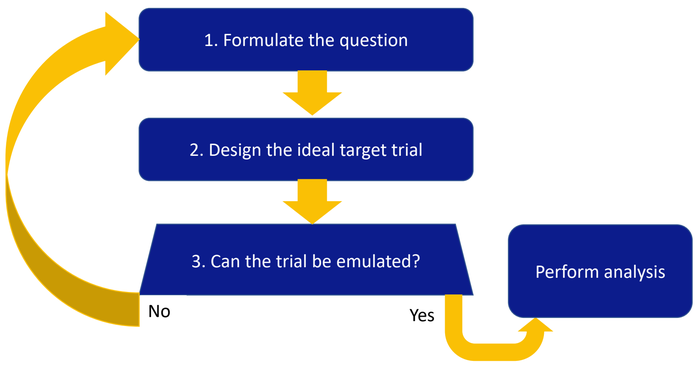
RCTs are sometimes not feasible, ethical or timely. Using observational data to emulate a target trial can return reliable treatment effects if specified correctly. [6]

Target trial emulation offer a framework to guide the investigator to be able to setup a target trial, in other words, what is the randomised experiment you wish to emulate?

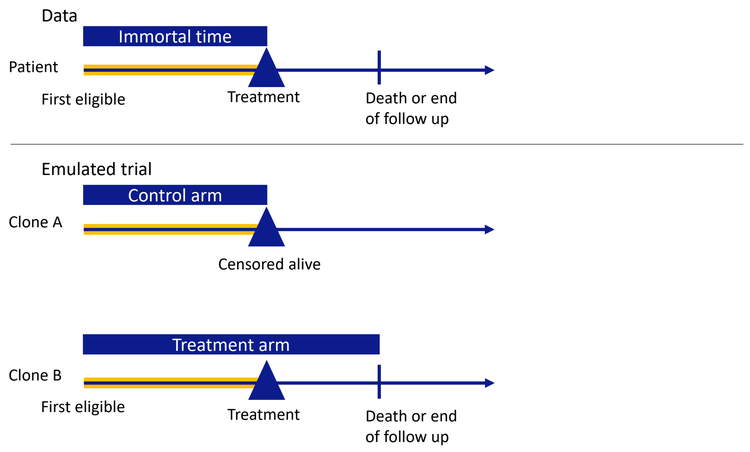
Firstly we describe the ideal target trial. Secondly, how the observational data can be used to emulate that target trial. [7]



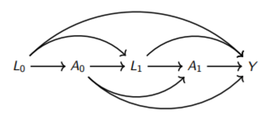
Target Trial methodology is an iterative process.



This study employs target trial methodology to test two protocols compared to a naïve analysis.



Clone and censor methodology was applied to omit any immortal time bias and prevent baseline confounding. Inverse probability of censoring weights were modelled to account for the selection bias, introduced from cloning and censor approach and time varying confounding.



Time-varying confounding affected by prior treatment

Longitudinal setting

We compared naïve and weighted Kaplan Meier (counterfactual) curves for the alternative treatment strategies.

Results

A naïve analysis of our cohort would suggest that ESAs yield no benefit at 6.5 years follow up.

Correcting for the risk of immortal time bias and accounting for time-varying confounding reveal that the actual impact of ESAs on the outcomes of interest depend on the study protocol.

Results for protocol 1 analyses suggest that ESAs have no survival advantage (HR: 1.05; 95% CI: 0.76 – 1.4) while under protocol 2 the ESAs had an important survival benefit (HR: 0.83; 95% CI: 0.54 – 1).

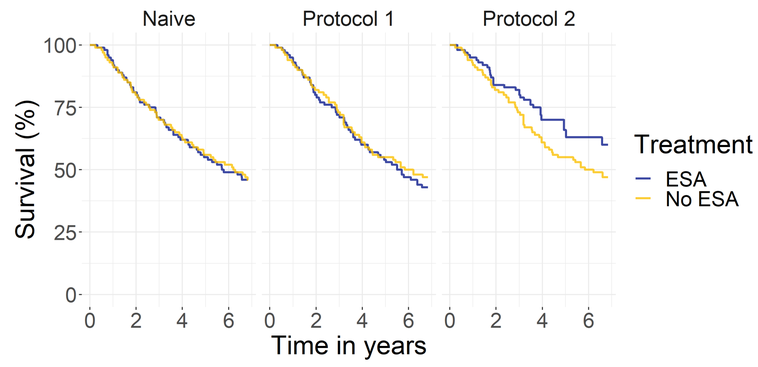


Figure 1: Displays Kaplan Meier curves for naïve analysis (left) and weighted Kaplan Meier curves protocol 1 (middle) and protocol 2 (right). The naïve analysis did not emulate a target trial and assess the same treatment strategy as the ideal trial Protocol 1 and 2 account for immortal time bias and time varying confounding.

Conclusion

This is the first study that uses a target trial emulation approach to evaluate intervention strategies in LRMDS.

Our work shows by example how to apply target trial emulation to real world data so that more reliable survival estimates are returned. This information can be used to help inform clinical and funding decisions.

Target trial emulation is another tool that can be used to estimate more accurate survival estimates when an RCT is not possible.

Acknowledgement

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References

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Table 1: Target trial emulation protocol showing the ideal trial protocol and two emulated protocols for different scenarios

Protocol Component	Ideal target trial	Emulated Trial: Protocol 1	Emulated Trial: Protocol 2
Eligibility Criteria	Diagnosis of intermediate-1 to low-risk MDS; treatment naïve; non-del(5q) MDS; hb<10g/dL and serum EPO<500mU/mL	Find point at which patients becomes first eligible using same criteria as in ideal trial.	Find point at which patients becomes first eligible using same criteria as in ideal trial.
Treatment Strategies	Intervention: initiation of ESAs at any dose within 1 months of becoming eligible for treatment. **Individuals will continue to take ESA.** Control: No initiation of ESAs during the study follow-up period. In both groups individuals can receive RBCT, GCFS and other non-MDS medications treatments after baseline.	Same as ideal trial **Individuals can discontinue ESAs at any time when indicated.**	Intervention: initiation of ESAs at any dose within 1 months of becoming eligible for treatment. **Individuals must continue to take ESA.** Control: No initiation of ESAs during the study follow-up period. In both groups individuals can receive RBCT, GCFS and other non-MDS medications treatments after baseline
Follow-up period	Start: From time of randomised treatment assignment End: - Death - Reach end of follow up period	Start: First point in time where patients meets eligibility criteria End: - Death - Dropout (loss to follow-up or withdraw from study) - Reach end of follow up period	Start: First point in time where patients meets eligibility criteria End: - Death - Dropout - Reach end of follow up period - **Stops taking ESA for people assigned to ESA group**
Outcome	Overall survival across follow up times and at 6 years	Same as ideal trial	Same as ideal trial
Casual contrast of interest	Intention to Treat effect/Per protocol	Per protocol effect	Per protocol effect
Analysis plan	Construct Kaplan-Meier Curves	Lack of randomisation means confounding exists. Use clone and censor approach to account for immortal time bias and balance groups at baseline Use Inverse Probability of Censoring Weights to account for selection bias introduced by cloning patients and time varying confounding Construct Weighted Kaplan-Meier Curves	Same as Protocol 1

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