**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.

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

**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?

We compared naive and weighted Kaplan Meier (counterfactual) curves for the alternative treatment strategies. We judged that ESAs yield no benefit at 6.5 years follow up.

**Results**

A naive 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).

**Conclusion**

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

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.

**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

<table>
<thead>
<tr>
<th>Protocol Component</th>
<th>Ideal target trial</th>
<th>Emulated Trial: Protocol 1</th>
<th>Emulated Trial: Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility Criteria</strong></td>
<td>Diagnosis of intermediate-1 to low-risk MDS; treatment naïve; non-del(5q) MDS; Hb&lt;10g/dL; and serum EPO&lt;500mU/mL</td>
<td>Find point at which patients becomes first eligible using same criteria as in ideal trial.</td>
<td>Find point at which patients becomes first eligible using same criteria as in ideal trial.</td>
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<tr>
<td><strong>Treatment Strategies</strong></td>
<td>Intervention: initiation of ESAs at any dose within 1 month of becoming eligible for treatment.</td>
<td>Individuals can discontinue ESAs at any time when indicated.</td>
<td>Individuals must continue to take ESA.</td>
</tr>
<tr>
<td><strong>Follow-up period</strong></td>
<td>Start: From time of randomised treatment assignment End: Death - Drop out: absence of follow-up</td>
<td>Start: First point in time where patients meets eligibility criteria End: Death - Drop out: absence of follow-up</td>
<td>Start: First point in time where patients meets eligibility criteria End: Death - Drop out: absence of follow-up</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Overall survival across follow up times and 6 years</td>
<td>Same as ideal trial</td>
<td>Same as ideal trial</td>
</tr>
<tr>
<td><strong>Causal contrast of interest</strong></td>
<td>Intention to Treat effect/Per protocol</td>
<td>Per protocol effect</td>
<td>Per protocol effect</td>
</tr>
<tr>
<td><strong>Analysis plan</strong></td>
<td>Construct Kaplan-Meier Curves</td>
<td>Use randomisation means confounding exists.</td>
<td>Use randomisation means confounding exists.</td>
</tr>
</tbody>
</table>

**Figure 1:** Displays Kaplan Meier curves for naïve analysis (left) and weighted Kaplan Meier curves protocol (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.