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Commentary

Time T - to - understand treatment response

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Commentary

Time *T*- to- understand treatment response

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In personalized medicine, understanding treatment effect heterogeneity in randomized controlled trials is essential. Exploring subgroups with better or worse treatment responses can reveal characteristics or pathways that differentiate responders from non-responders.

In the field of obstructive lung diseases, interventions targeting exacerbations often use total event rates as the primary outcome. However, as this averages the number of events across all participants, it remains undiscernible whether a treatment effect is broadly distributed over the studied population, or driven by specific subgroups.

Time-to-first-event analyses are valuable complementary outcomes, as equal weight is assigned to all participants in reaching the studied outcome. Although participants are censored after their first event, the timing of first events and pattern of time-to-first-event curves can provide critical insights into response dynamics. Since actual exacerbations are the best predictor of future events, patients with a short time to their first event are -on a group level- more likely to experience subsequent exacerbations at shorter intervals.[1,2] With this in mind, particularly when time-to-first-event curves cease to diverge during follow-up, meaningful assumptions can be made.

We propose a framework in which integrating both analyses can help to better understand treatment responses on recurrent event rates and potentially identify treatable traits.

The Total Event Rate Curve: Insights into Treatment Response Dynamics

The total event rate curve, represented by the cumulative mean number of events, reveals the nature and sustainability of treatment responses. Only when the curves for treated and untreated groups continue to diverge, the treatment has a sustained effect, at least during the time of the follow-up (figure 1, plot A). If the curves become parallel or reconverge (figure 1, plot B or C), the treatment delays early events in the treated group, but without affecting the overall rate of subsequent events, which may warrant a reassessment of the value of the intervention.

Integrating Time-to-First-Event data with recurrent event analyses

Integrating cumulative total event rates with the time-to-first-event curves offers a more nuanced understanding of the dynamics underlying overall treatment effects. Steadily diverging total event rate curves might be assumed to correlate with continuous divergence in time-to-first-event curves throughout follow-up (*figure 1, scenario A + D*), yet this is not necessarily so. Time-to-first event curves may stop diverging or even reconverge at a specific timepoint, call this timepoint ***T***. This reflects a "depletion of susceptibles"-phenomenon. Initially, a steeper incline in incidence of first events is expected in control patients, as their high risk profile remains untreated. However, as fewer susceptible patients remain at risk, the probability of events will decrease and curves will cease to diverge from treated patients.[3] Meanwhile, total event rate curves may continue to widen beyond ***T*** if the treatment maintains an effect on recurrent events (*figure 1, scenario A + E or A + F*).

As an example, consider the NOTUS trial [4], which investigated Dupilumab for preventing COPD exacerbations. Over 52 weeks, the mean exacerbation rate was 0·86 in the dupilumab group versus 1·30 in the placebo group (rate ratio 0·66; p<0·001). Early in the trial, time-to-first-event curves diverged between treated and untreated groups. However, by week 16, divergence ceased, and the difference remained constant for the remainder of the 52-week follow-up. Despite this, the cumulative mean total event rate curves continued to diverge steadily, indicating that the treatment effect was further driven by a reduction of recurrent events.[3]

Plotting the cumulative incidence of first events (which is not completely similar to time-to-first-event) alongside the total event rate curve, reveals additional insights (***figure 1, plots H to I***). Firstly, the ratio of the orange to blue area approximates the rate ratio driven by recurrent events, with a smaller ratio indicating a stronger treatment effect on recurrent events. Secondly, timepoint ***T*** – if identified in the time-to-first-event curves- marks the point beyond which further divergence in total event rates is driven solely by treatment effects in patients who already had at least one event. Therefore, the earlier ***T*** appears in the trial, the more likely the overall intervention effect will be driven by recurrent event reduction. Assuming first and recurrent events share similar pathophysiological mechanisms, an early ***T*** should prompt subgroup analyses, as the observed effects may be driven by smaller subgroups that strongly express the pathways targeted by the treatment.[5,6] We expect that for the NOTUS trial, people with higher baseline levels of exhaled Nitric Oxide (> 20ppb) benefited most from Dupilumab both on primary and recurrent events.[7]

Time-to-First-Event data for subgroup identification

Timepoint *T* may also mark a transition for the risk of an event. In the placebo arm, patients with an event before *T* likely have a higher risk profile than those with their first event after *T* (respectively 22% vs. 20% of patients in NOTUS, with *T* at 16 weeks). Subjects experiencing no events during the trial presumably have the lowest baseline risk (58% in NOTUS). Comparison of baseline characteristics of *T*-defined subgroups could indirectly identify descriptors for both the observed treatment effect and event risk. In fact, if such traits are present (for instance high FeNO), one would expect them to be more prevalent in the $t < T$ placebo group as compared to the $t > T$ placebo group, in which a treatment effect on first event is no longer observed. Similarly, the prevalence of such traits should be lower in the $t < T$ intervention group compared to the $t < T$ placebo group, as the treatment shifts patients with these traits beyond *T*.

Conclusion

Total event rate curves may keep diverging throughout a trial, while time-to-first-event curves show only small differences and cease diverging at a timepoint *T*. Identifying *T* may provide important insights into treatment effects on recurrent events and characteristics of patient subgroups, which drive event risk but also treatment effects.

Contributions

WJ: Initial concept, writing, critical revisions. IG: Critical concept design, original draft text and figures, critical revisions. HH: Critical concept design, critical revisions. MDV: critical revisions.

Declaration of interests

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Figure

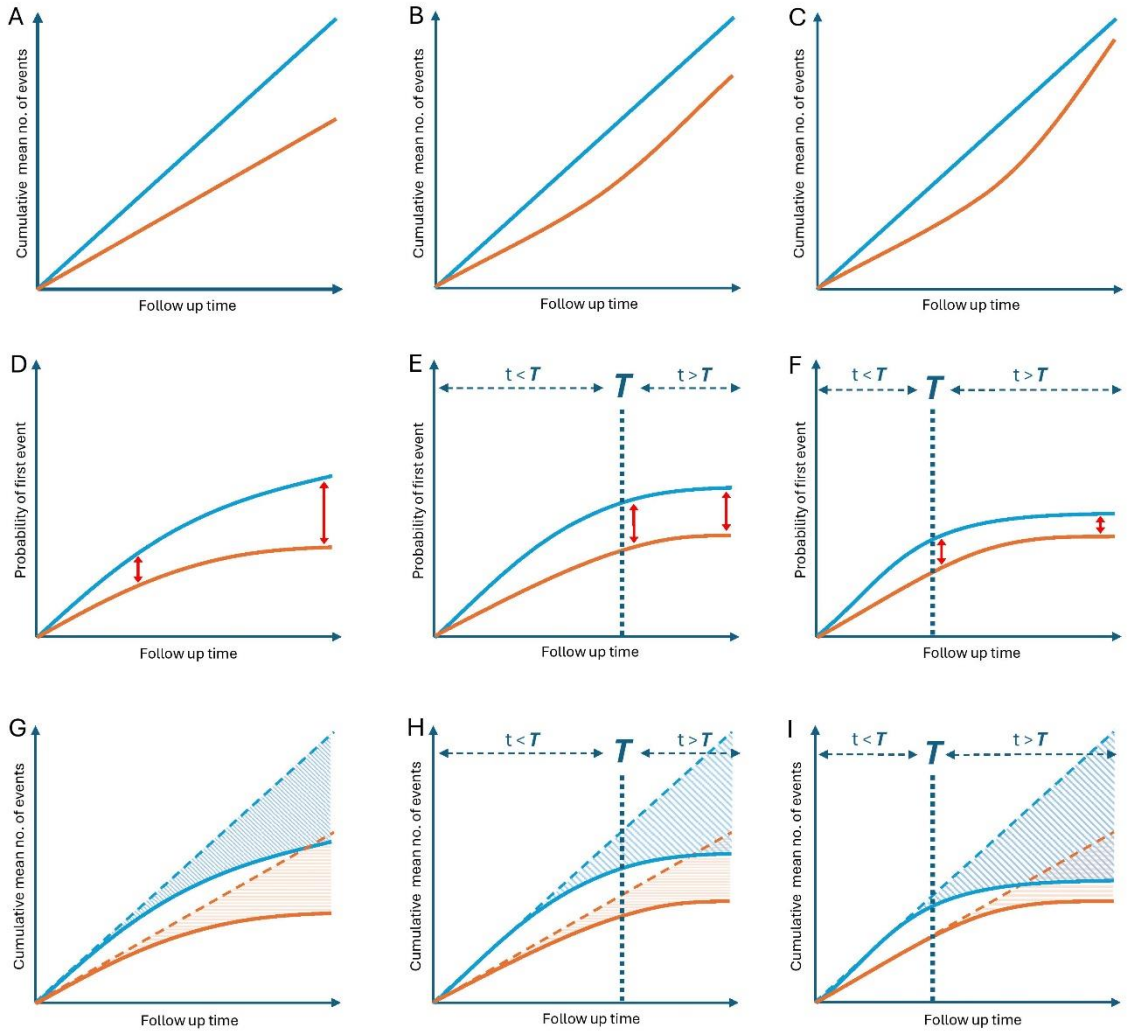


Figure legend

Different scenarios for cumulative mean number of total event curves (A-C), time-to-first-event curves (Kaplan Meier estimate) (D-F) and combined cumulative number of first and total event curves (G-I) of intervention (orange) and control (blue) arms of a randomized controlled trial. Total event rates may keep diverging throughout a trial (A vs B/C), while time-to-first-event curves cease diverging or reconverge at timepoint ***T*** (A+D vs A+E/F). The orange over blue area ratio approaches the cumulative treatment effect on recurrent events. Early occurrence of ***T*** (F/I) suggests the intervention effect is primarily driven by recurrent event reduction.

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