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What can we learn from one million completed daily diaries about patient compliance, burden and usefulness of that PRO?

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Abstract

Little is known about overall trends in compliance and the amount of time different patients spent completing daily patient-reported outcome (PRO) symptom diary in clinical trials. This work analyzes 1500 patients randomized across three trials (Table 1), who collectively spent over four person-years completing almost one million daily diaries. By combining comprehensive timestamp data collected from Clario and patient-level data collected from these trials, the results show daily PRO compliance decreases linearly with time throughout the trial, but the rate of decrease is highly dependent on age. The response time (i.e. time spent completing the PRO) plummets in the first month of the study and further decreases until the end of the trial but at much lower rate. Older patients take longer time to complete the PROs.

Introduction

- A universal rollout of ePRO devices in AstraZeneca's clinical trials calls for detailed analyses of how PRO completion impacts different patients.
- ePRO timestamps, along with clinical data, allows tracking patient compliance and time spent on completing PROs (response time)
- Fatigue can be indirectly measured through various factors, e.g. careless responder metrics, procrastination (for ePRO completed at home during a time window) and information content.

Methods

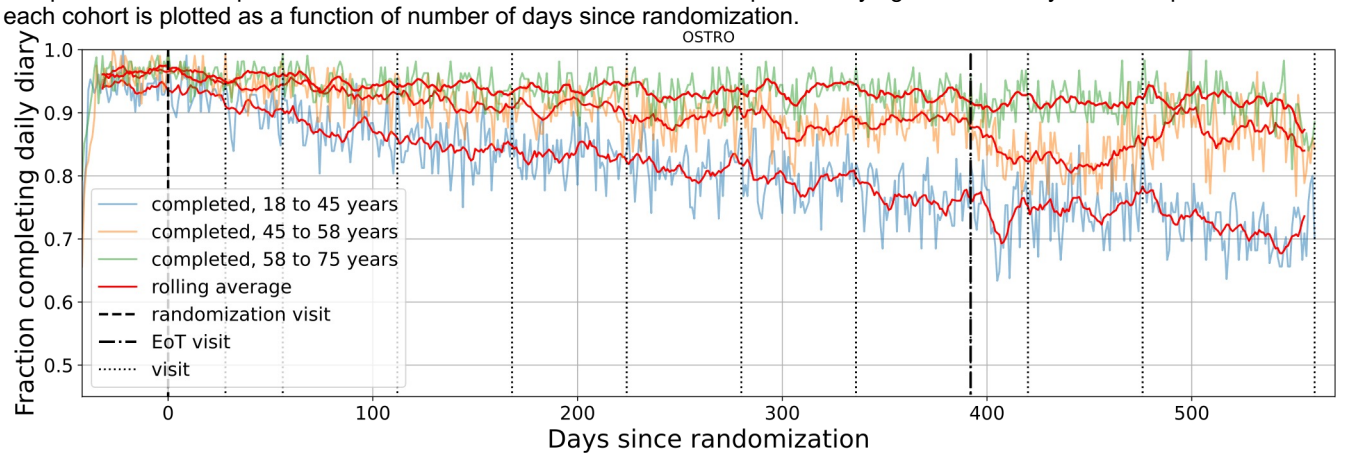
- Daily PRO start and end timestamps for 1463 randomized patients were extracted from three respiratory trials (Table 1) and linked to the respective clinical data.
- Logistic regression was used to identify unbiased coefficients associated with compliance.
- A General Linear Model with log-logistic regression to response time was fitted for each model separately, with the coefficients and 99.9% confidence intervals in Figure 2.

Table 1 clinical studies used in this work:
Only randomized patients were used for in the analyses.

Study	Title	Patients
OSTRO[1] NCT03401229	"Efficacy and Safety Study of **Benralizumab** for Patients With **Severe Nasal Polyposis**"	360 randomized, 35 discontinued, 10 due to AE Per patient (median): 588 days, 450 diaries, 5.6h total time
SOURCE[2] NCT03406078	"Study to Evaluate the Efficacy and Safety of **Tezepelumab** in Reducing Oral Corticosteroid Use in Adults With Oral **Corticosteroid Dependent Asthma**"	143 randomized, 8 discontinued, 2 due to AE Per patient (median): 396 days, 378/376 morning/evening diaries, 31.6h total time
NAVIGATOR[3] NCT03347279	"Study to Evaluate **Tezepelumab** in Adults & Adolescents With **Severe Uncontrolled Asthma**"	960 randomized, 74 discontinued, 19 due to AE Per patient (median): 408 days, 373/366 morning/evening diaries, 28.2h total time

Results

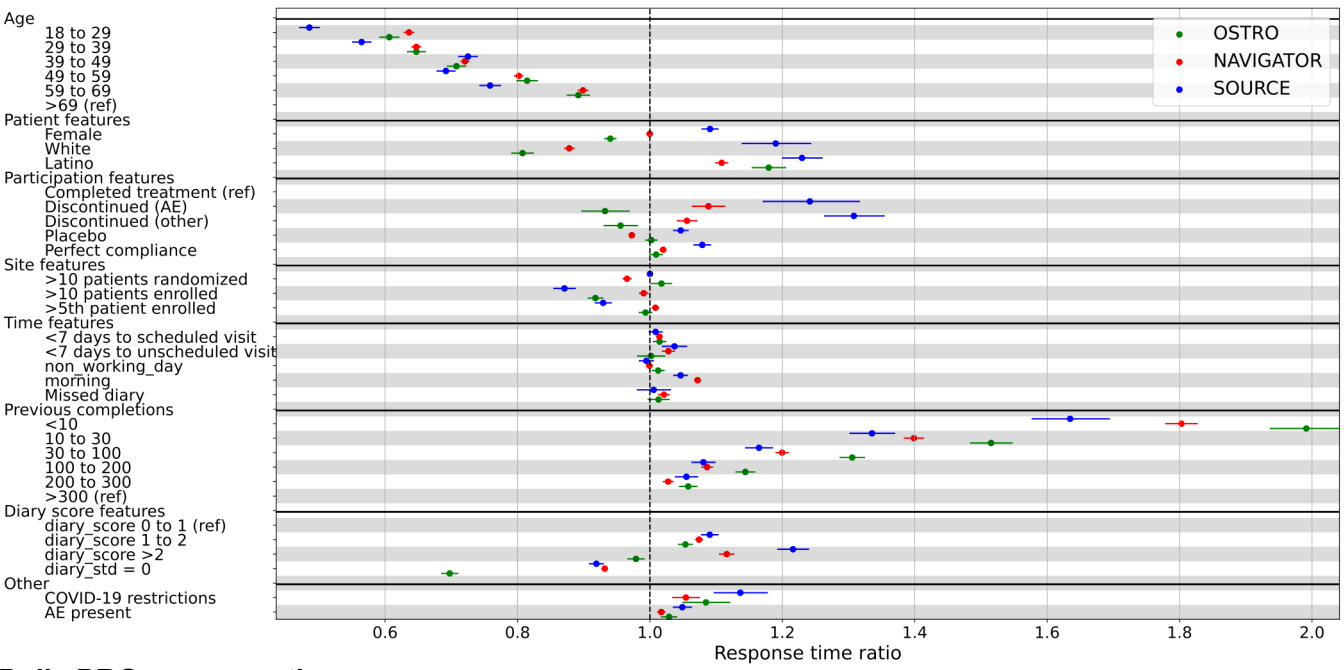
Figure 1 Daily PRO compliance rates in OSTRO study:
325 patients who completed the full treatment were divided into three quantiles by age and the daily PRO compliance across each cohort is plotted as a function of number of days since randomization.



Daily PRO compliance

Compliance decreases linearly in time since randomization, but the rate of decrease is higher in younger patients (Figure 1). It is highly correlated with the 14-day pre-randomization compliance and morning assessments have higher compliance than evening ones (data not shown). Adherence to the daily PROs increases as the date of the scheduled visit approaches – this effect is more visible in the lower compliance cohorts in Figure 1.

Figure 2 Daily PRO compliance rates in the OSTRO, NAVIGATOR and SOURCE studies:
Parameters of the Generalized Linear Model with log-logistic noise distribution for each study. Only treatment period and randomized patients were included. Response time is the difference between the end and start timestamps.



Daily PRO response time

Response time is very dependent on age and experience (i.e. number of previous completions of the PRO). Older patients can take up to 3 times longer to complete the PRO on average (Figure 2). The response time (i.e. time spent completing the PRO) plummets in the first month of the study and further decreases until the end of the trial but at much lower rate. Morning assessments, presence of any adverse events and concurrent COVID-19 restrictions in the country consistently increase the time it for PRO completion. Finally, low answer dispersion ("diary_std=0" in Figure 2) is strongly associated with very short response time suggesting that it might be due to straight-lining.

Future directions

- A systematic analyses of potential straight-lining (i.e. selecting same response option on all questions) or other measures of careless response as a sign of patient fatigue
- Analysis of information content of the responses to determine if daily PROs still provide discriminative information in long trials
- Analysis of procrastination in completing longer PROs at home in a window of time as an indirect measure of patient fatigue
- Exploration of the same data type in Oncology and CVRM studies

Conclusions

- Compliance with a daily PRO is associated strongly with patient's age, time elapsed from randomization, proximity to a visit and whether they ultimately discontinued treatment
- Response time is also associated with patient's age and their experience with the PRO
- Tracking these two variables might be helpful in identifying patients at-risk of discontinuation

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References
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