Follow-up quantification in time to event clinical trials

Oncology estimand WG session at PSI 2023 conference London

Lynda Grinsted

14th June 2023

Estimands in Oncology Working Group
Status

- As of 19th April 2023, the working group
  - has 99 members (37 from Europe, 52 from US, and 10 from Asia) representing 48 companies / institutions,
  - regularly interacts with eight Health Authorities globally,
  - regularly organizes sessions and presents at conferences,
  - has started to interact with academic colleague

- Regularly updated list of Publications and Events with contributions from the working group are available on www.oncoestimand.org.

Estimands in Oncology Working Group Subteams and taskforces

Estimands engagement*	Principal stratification in clinical trials*	Patient-reported outcomes* TODAY	Conditional vs. marginal effects*	Time to event endpoints with prognostic or predictive biomarker subgroups* TODAY
Real-world data and estimands	Estimands for Safety	Duration of responses ^	Quantification of follow-up ^ TODAY	Early development estimand nexus (EDEN) ^ TODAY
Treatment Switching^ TODAY	Causal estimands^	Censoring^	Hematology^	Solid tumors^

*Taking new members

^ Complete

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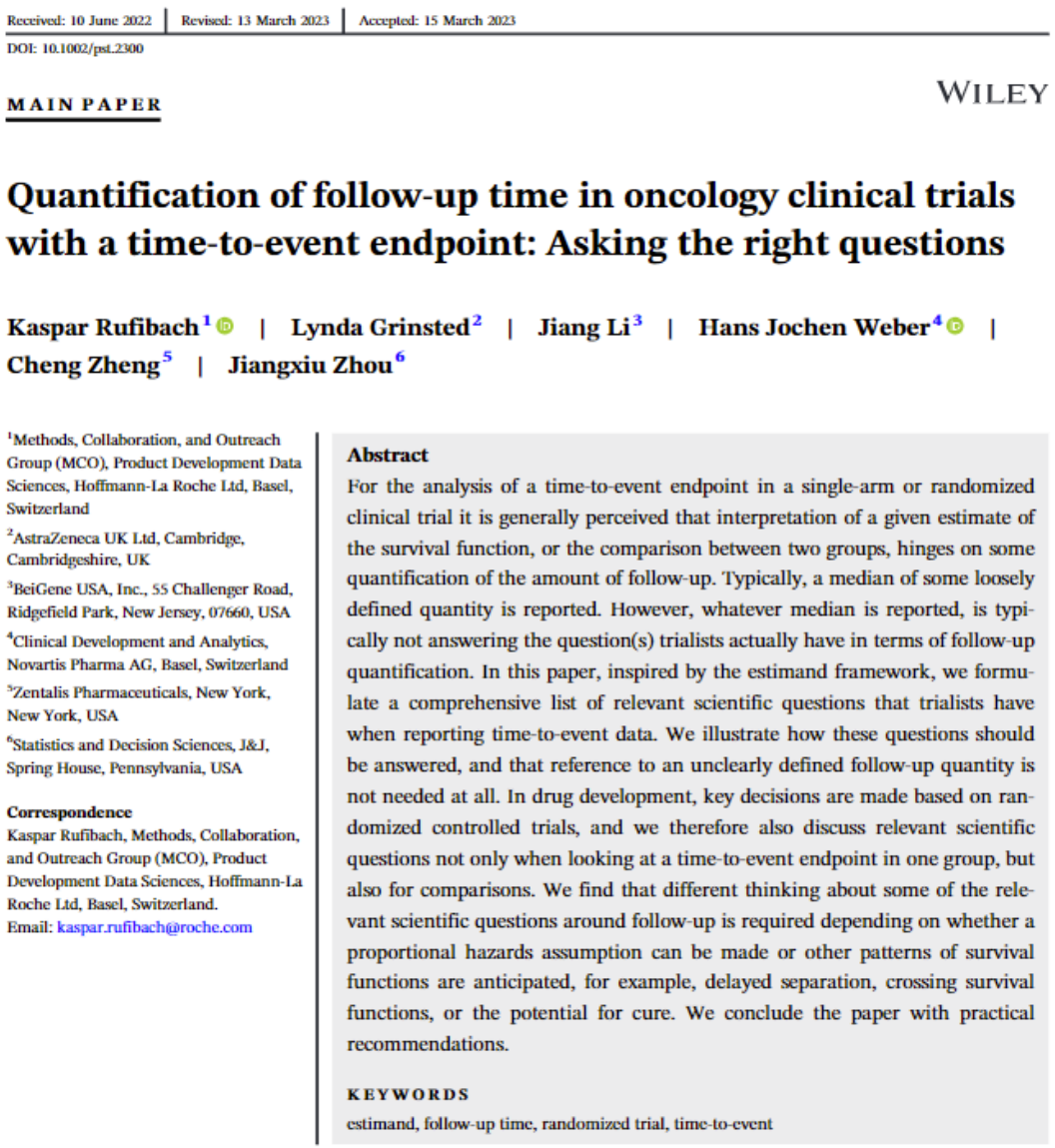
  - Jiangxiu Zhou
  - Cheng Zheng



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MAIN PAPER

WILEY

Quantification of follow-up time in oncology clinical trials with a time-to-event endpoint: Asking the right questions

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Abstract

For the analysis of a time-to-event endpoint in a single-arm or randomized clinical trial it is generally perceived that interpretation of a given estimate of the survival function, or the comparison between two groups, hinges on some quantification of the amount of follow-up. Typically, a median of some loosely defined quantity is reported. However, whatever median is reported, is typically not answering the question(s) trialists actually have in terms of follow-up quantification. In this paper, inspired by the estimand framework, we formulate a comprehensive list of relevant scientific questions that trialists have when reporting time-to-event data. We illustrate how these questions should be answered, and that reference to an unclearly defined follow-up quantity is not needed at all. In drug development, key decisions are made based on randomized controlled trials, and we therefore also discuss relevant scientific questions not only when looking at a time-to-event endpoint in one group, but also for comparisons. We find that different thinking about some of the relevant scientific questions around follow-up is required depending on whether a proportional hazards assumption can be made or other patterns of survival functions are anticipated, for example, delayed separation, crossing survival functions, or the potential for cure. We conclude the paper with practical recommendations.

KEYWORDS

estimand, follow-up time, randomized trial, time-to-event

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Oncology publications include varying definitions of follow-up for T2E endpoints such as PFS and OS

"As of May 9, 2016, the median duration of follow-up was 11.2 months (range, 6.3 to 19.7)"

- **Betensky (2015) found reporting to be unclear**

  'Of the 60 articles (37% of the 161 Original Reports) that reported a median follow up time, 34 (57%) did not specify what was meant by "median follow up."

  'None of these papers interpreted their reports of follow-up'

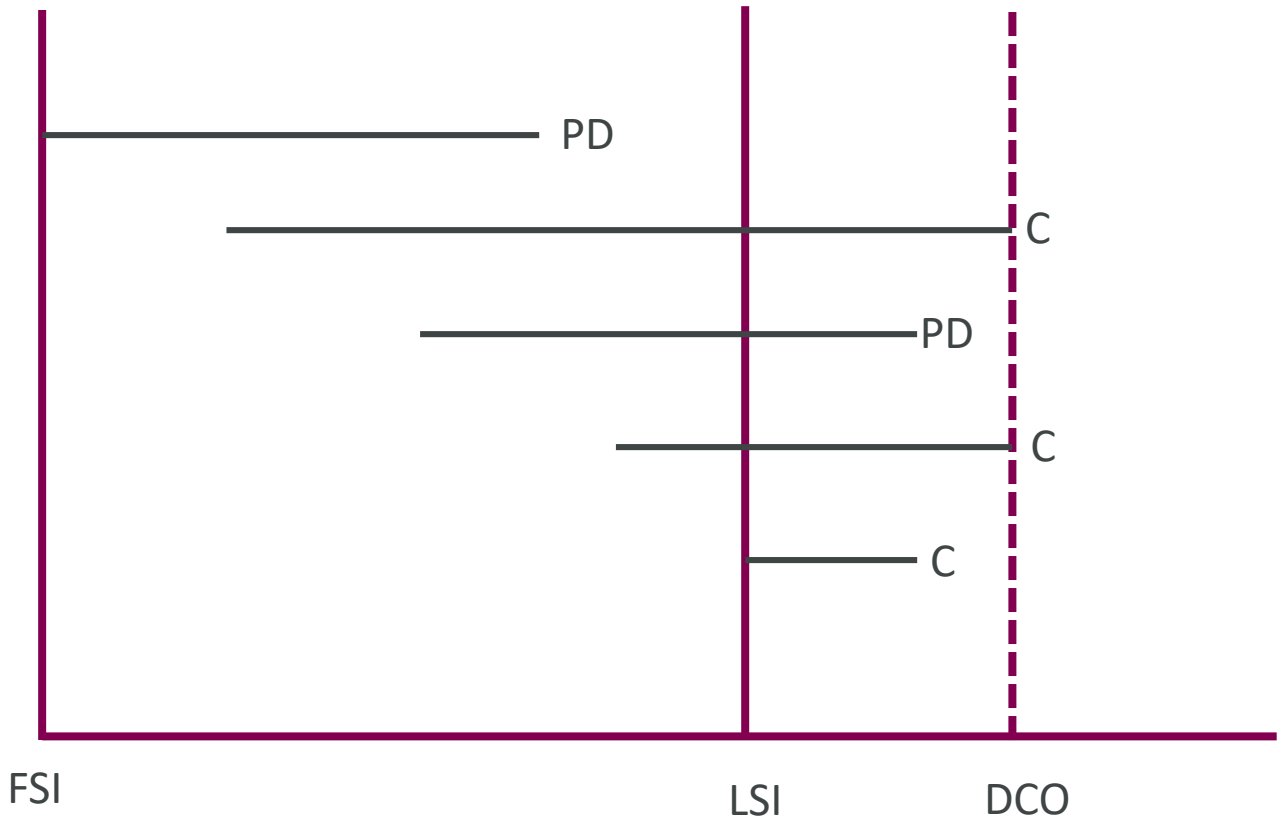
- **CONSORT recommends including median follow-up but without a definition**

  The length of follow-up is not always a fixed period after randomisation. In many RCTs in which the outcome is time to an event, follow-up of all participants is ended on a specific date. This date should be given, and it is also useful to report the minimum, maximum, and median duration of follow-up.[200] [201]

What is the question of interest?

- **Clinical trial question of interest**
  - E.g, Hazard ratio for drug X v drug Y of progression or death from any cause in patients with <cancer type> irrespective of discontinuation of interventional treatment, start of subsequent anti-cancer therapy or clinical progression.
- **Follow-up question(s) of interest (Shuster 1991)**
  1. "Maturity" of the estimated survival function.
  2. "Stability" of the estimated survival function.
  3. Time interval where KM estimate is "valid".
  4. "Quality" of follow-up.

Example definitions of follow-up



Number	Term
1	Observation time regardless of censoring
2	Observation time for those censored
3	Time to censoring
4	Time to CCOD, Potential follow-up
5	Known function time
6	Korn's potential follow-up time
7	Potential follow-up considering events

FSI=First Subject In, LSI=Last Subject In, DCO=Data Cut Off, C=Censored, PD=Progressive disease

Answering the follow-up questions of interest

Question of interest	One sample	Two samples and proportional hazards	Two samples and non-proportional hazards
PRECISION	KM confidence bands	Hazard ratio confidence interval	eg RMST
RELIABILITY	KM confidence bands, no. at risk	Assessment of proportional hazards assumption	-
STABILITY	Eg assume censored observations to be events or censor at latest event time	IF PH, HR should not change	Look at extreme scenarios
INFORMATION	Power	Information fraction	Depends on effect measure
CENSORING PATTERN		Censoring distribution by arm	Censoring distribution by arm

Recommendations

1. Be clear on the scientific questions you want to answer.
2. Make clear that no single number, can say everything about “follow-up”, answer all the relevant questions trialists have, or allow comparisons across trials.
3. Give survival estimates for all treatment groups
4. Discuss precision, stability, information, and potential assumptions separately for any quantity of interest
5. Estimate censoring distribution for each treatment arm
6. Describe accrual stating FSI and LSI (and the distribution if not uniform)
7. Give DCO
8. Consider describing distribution of censoring reasons (administrative vs. LTFU)
9. Add patient numbers still at risk below the KM plot
10. If required to present follow-up, define how it is computed. Time to censoring is considered most informative

References

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