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Considerations for Censoring Methods Used to Reconstruct Pseudo Patient-Level Data From Kaplan–Meier Curves

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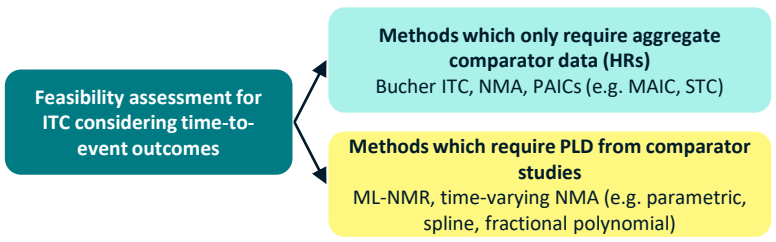
INTRODUCTION

- The reconstruction of pseudo patient-level data (PLD) plays a critical role in accurately conducting indirect treatment comparisons (ITCs) using published time-to-event graphs, if such information is not explicitly provided in the publication
- In some cases, reconstructed PLD are necessary to estimate hazard ratios (HRs) that may not be reported in a publication. In other cases, reconstructed pseudo PLD are required to conduct the ITC. As time-varying comparative analyses gain more popularity in the health economics landscape, aiming to address violations of the proportional hazard assumption, reconstructed PLD for comparator trials will often become a necessity, as it is not standard practice to publish such data
- Figure 1 illustrates data requirements for common ITC methods. Notably, multi-level network meta-regression and time-varying network meta-analyses (NMA), highlighted in yellow, require PLD or pseudo PLD for analysis of time-to-event comparator outcomes[1,2,3]

Figure 1. Data requirements for common ITC methods



Key: HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; ML-NMR, multilevel network meta-regression; NMA, network meta-analysis; PAIC, population-adjusted indirect comparison; PLD, patient-level data; STC, simulated treatment comparison.

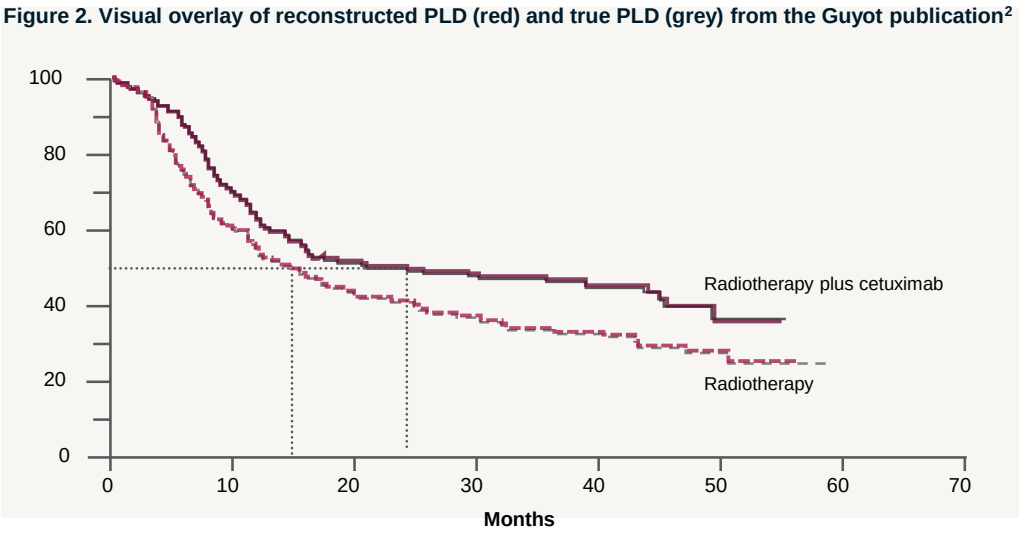
- The Guyot method[4] is a widely used algorithm that assumes censoring events follow a uniform distribution. However, in practice, censoring events where loss to follow-up is due to changes in treatment regimen or adverse events may not follow a uniform distribution.
- PLD have previously been reconstructed[5] using various censoring allocation methods. It was found that censoring placement had minimal impact on the estimated relative effect (i.e. HR), but variation was observed in 10-year restricted mean survival time between choice of censoring method. Thus, our aim is to consider how censoring allocation should be handled in pseudo PLD reconstruction for the methods highlighted in yellow in Figure 1. As ITC developments have advanced since the Guyot method[4] was developed, advancements in methods for pseudo PLD should also be considered

OBJECTIVES

How are censoring times generated by various reconstruction methods?

- This exercise aimed to:
  - Investigate censoring allocation choice in pseudo PLD reconstruction methods and assess potential impact on the accuracy of the reconstruction
  - Provide considerations on selecting an appropriate reconstruction method based on type of ITC analysis

Figure 2. Visual overlay of reconstructed PLD (red) and true PLD (grey) from the Guyot publication[2]



Key: PLD, patient-level data.

METHODS

Literature review of recent PLD reconstruction methods

- A literature review was conducted in April 2024 to identify various methods used for generating reconstructed PLD from Kaplan–Meier curves with either a constant relative hazard or a time-varying HR. Key search terms included: 'reconstruct', 'individual patient data', 'patient level data', 'KM data algorithm', 'censoring allocation', 'Kaplan-Meier', 'summary survival data', 'improved survival data reconstruction' and 'censoring points in reconstructed patient level data'
- Various PLD reconstruction methodologies were assessed, focusing on identifying differences in reconstruction from the well-known Guyot algorithm.[4] Considerations of publications explored for the purpose of this exercise were restricted to:
  - More recent literature (methods published after 2010)
  - Publications explicitly describing the reconstruction methodology used, including an algorithm flow chart or estimation process
  - Publications reporting a simulation validation phase as a part of the results section
- The literature review was aimed at expanding the Wan et al.[6] publication, which compares implications of pseudo PLD reconstruction and censoring allocation between two methods (Guyot and Hoyle) but does not include the two methods developed after 2013
- Methodologies were summarized, data requirements and assumptions were compared, and benefits and limitations were highlighted to help inform choice of PLD reconstruction method based on evidence availability and project context

RESULTS

- The review yielded three reconstruction methods[7,8,9] that were published between 2011 and present day. The review includes an algorithm flow chart or estimation process that is reproducible, and it contains a simulation validation to ensure results were comparable to the simulated time-to-event data being reconstructed. The review excluded any publications that reported performing one method of reconstruction for the purpose of an ITC, as the use of such analysis did not provide information that was suitable for the purpose of comparing methods
- Two of the publications (Lui and Rogula) describe recent modifications to the Guyot algorithm, while Hoyle et al. was discovered as a result of the Wan et al.[6] comparison publication. Despite the method being published the year before Guyot, the method is within the scope of interest for the exercise
- An overview of the methodologies used to reconstruct PLD, compared with the Guyot algorithm, is shown in Table 1. The review focused on highlighting benefits as described in the respective publications

Table 1. Summary of reconstruction algorithm and positive implications of choice

Publication	Methodology summary	Key benefit of methodology
Guyot et al. (2012)[4]	Iterative algorithm based on KM estimation method maps from user-generated digitized curves back to KM data by finding numerical solutions to the inverted KM equations, using available information on a number of events	Well-established and cited throughout HTA documentation, including NICE and EU JCA guidelines[1,2]
Hoyle et al. (2011)[7]	Time, survival probability and number at risk are added by the user into a Microsoft Excel template to estimate the underlying PLD. The fitted curve is estimated through maximization of the likelihood function	Ability to generate pseudo PLD when only summary survival data are available. Achieves similar bias and mean square error when comparing mean survival time with true PLD
Liu et al. (2021)[8]	Modified iterative algorithm based on KM estimation method algorithm, all in one software with relaxed data input requirements compared with the Guyot approach	R package PLD from KM and accompanying web-based Shiny application can extract data coordinates without requiring a separate KM tracing tool
Rogula et al. (2022)[9]	The location and number of censoring times are not estimated by the algorithm; they are entered as data inputs to the algorithm after being digitized by the user	Extractable censoring times are incorporated into the reconstructed data exactly as specified

Key: HTA, health technology assessment; PLD, patient-level data; JCA, joint clinical assessment; KM, Kaplan–Meier; NICE, National Institute for Health and Care Excellence; PLD, patient-level data.

- Table 2 compares the data requirements and censoring-specific considerations for each methodology

Table 2. Input requirements and assumptions required for reconstruction methodologies

Publication	Input requirement	Number at risk	Censoring considerations
Guyot et al.[4]	▪ Data extraction of KM trace ▪ Number at risk table	Required*	Censoring following a uniform distribution between intervals of known number at risk tables
Hoyle et al.[7]	▪ Data extraction of KM trace ▪ Number at risk table	Required	Rate of censoring is constant over defined censoring intervals. Assumes censorships occur in middle of each quarter time interval
Liu et al.[8]	▪ Image of KM plot from publication	Not required	Censoring following a uniform distribution within modified proper boundary condition for the number of intervals (to prevent poor estimations in some scenarios)
Rogula et al.[9]	▪ Data extraction of KM trace, coordinates specifying tail of curve ▪ Total patient count ▪ Censoring times (if provided)	Not required	Incorporating censoring times exactly as they are marked and avoiding making assumptions about the distribution of censoring times

Key: KM, Kaplan–Meier.
Note: *If number at risk table is not available, the algorithm can run as long as number of patients at t = 0 is provided.

- The Hoyle et al. method indicates improvement in curve fit using the number of censorships and events in each time interval of quarter length. However, this is only feasible when number at risk is provided in the comparator population. Similarly for the Liu et al. method, accuracy under high and low censoring rates was only found to be guaranteed when number of patients at risk was reported. The benefit of the method established by Rogula et al. is reduced in cases where the graph does not include marks/ticks for censoring, or such markings are not distinguishable
- The limitations of these methods may help readers decide which method to implement for PLD reconstruction based on the publication data available. Despite no clear guidelines on which censoring allocation is most accurate, it is valuable to consider the implications of the censoring assumption in each method

CONCLUSIONS

- When there is extensive censoring observed in the data, and the proportional hazards assumption does not hold, the choice of algorithm should aim to reflect the event and censoring times of the patient population
- To generate a best practice for choice of digitization method based on censoring data assumptions, a simulation study comparing the different methods would be useful to determine whether there are significant differences due to method choice
- When deciding whether to implement newly published methods for PLD reconstruction, evidence availability and implications of censoring assumptions should be examined. Characteristics of input requirements, clarity of Kaplan-Meier curve and nature of censoring in the study should all be factored into the choice of PLD reconstruction method

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