Population pharmacokinetic modeling to assess the non-linear increase in exposure following increasing doses of rifampicin

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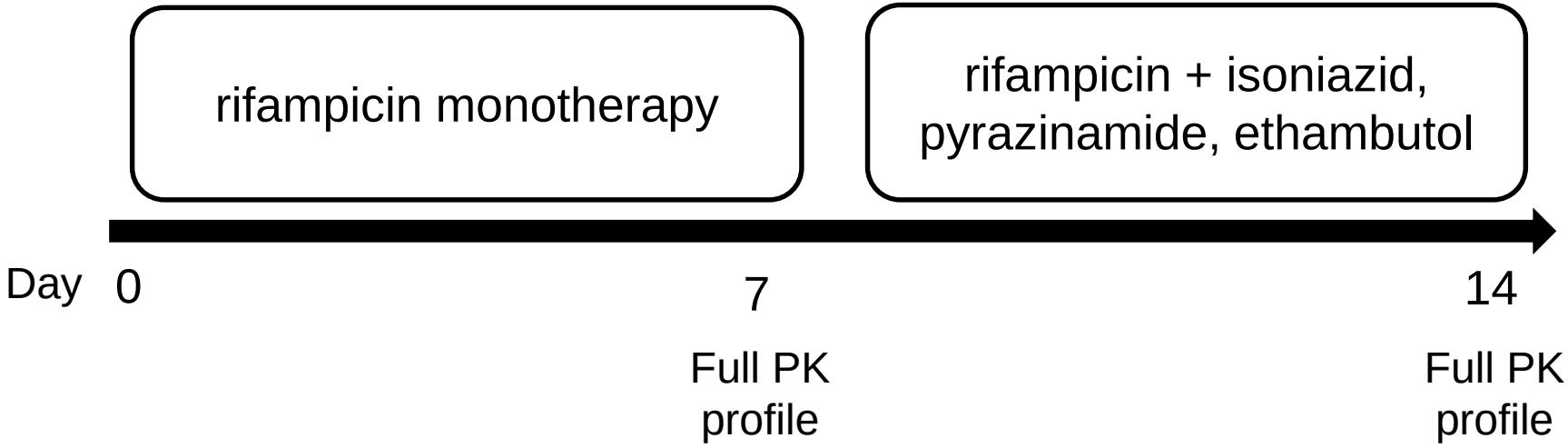
Rifampicin

- Recommended dose is 10 mg/kg[1]
- The selection of this dose did not adhere to current dose selection standards
- Accumulating evidence suggest that increasing the dose may reduce treatment time for tuberculosis (TB)
- Rationale for the PanACEA consortium to conduct the HIGHRIF1 trial[2] – a multiple dose rising trial to establish the maximum tolerated dose of rifampicin
  - A study assessing short-term safety, pharmacokinetics (PK) and pharmacodynamics (PD) of high doses of rifampicin

[1]WHO, The treatment of tuberculosis guidelines, 2010
[2]Boeree *et al*. Am J Respir Crit Care Med 2015

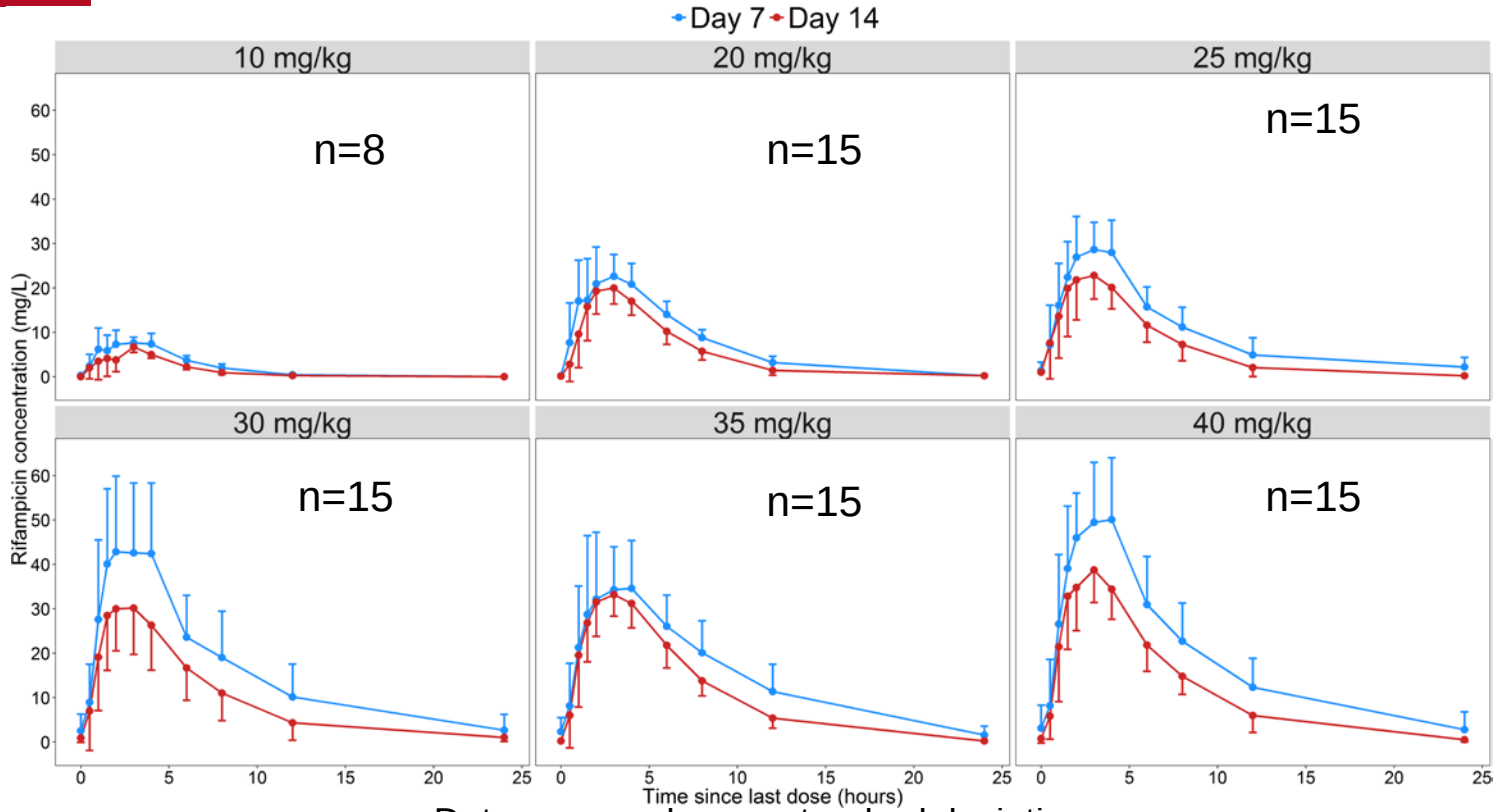
The HIGHRIF1 trial

- 83 adult pulmonary TB patients
  - A reference arm receiving 10 mg/kg (n=8)
  - 5 experimental arms receiving 20, 25, 30, 35 and 40 mg/kg (n=15/arm)



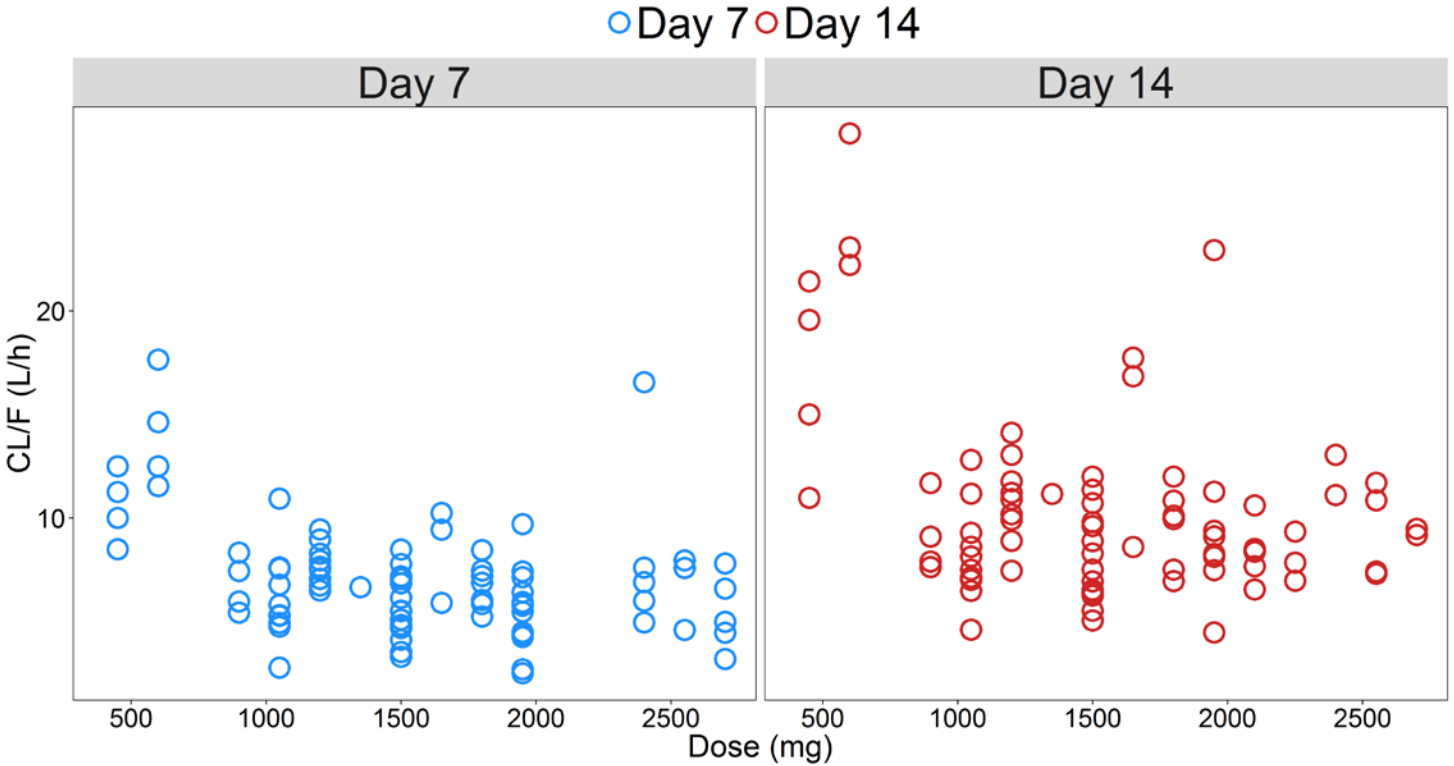
Rifampicin conc vs time

at Days 7 and 14 after different dose levels



Dots = mean, bars = standard deviation

NCA-based CL/F vs dose



NCA = non-compartmental analysis, CL/F = apparent clearance

Objective

Quantify the non-linearity in exposure including time-dependent CL/F (auto-induction) observed in the HIGHRIF1 trial using a non-linear mixed effects modeling approach in order to:

- Predict which PK parameters cause the non-linearity and their relationship to drug concentration and/or dose
- Predict exposures continuously over time
  - Clinical trial simulations
  - Forecast exposure in individual patients which may aid in therapeutic drug monitoring (TDM)

Model development

- All data simultaneously modeled using a non-linear mixed effects approach
- Starting model was a previously developed population PK model for rifampicin[1]
  - Model includes an enzyme turn-over model accounting for auto-induction
- Structural model
  - 1- vs 2-compartment disposition models
  - Absorption models; with/without lag-time parameter and transit compartment model

[1]Smythe *et al*. AAC 2012

Model development

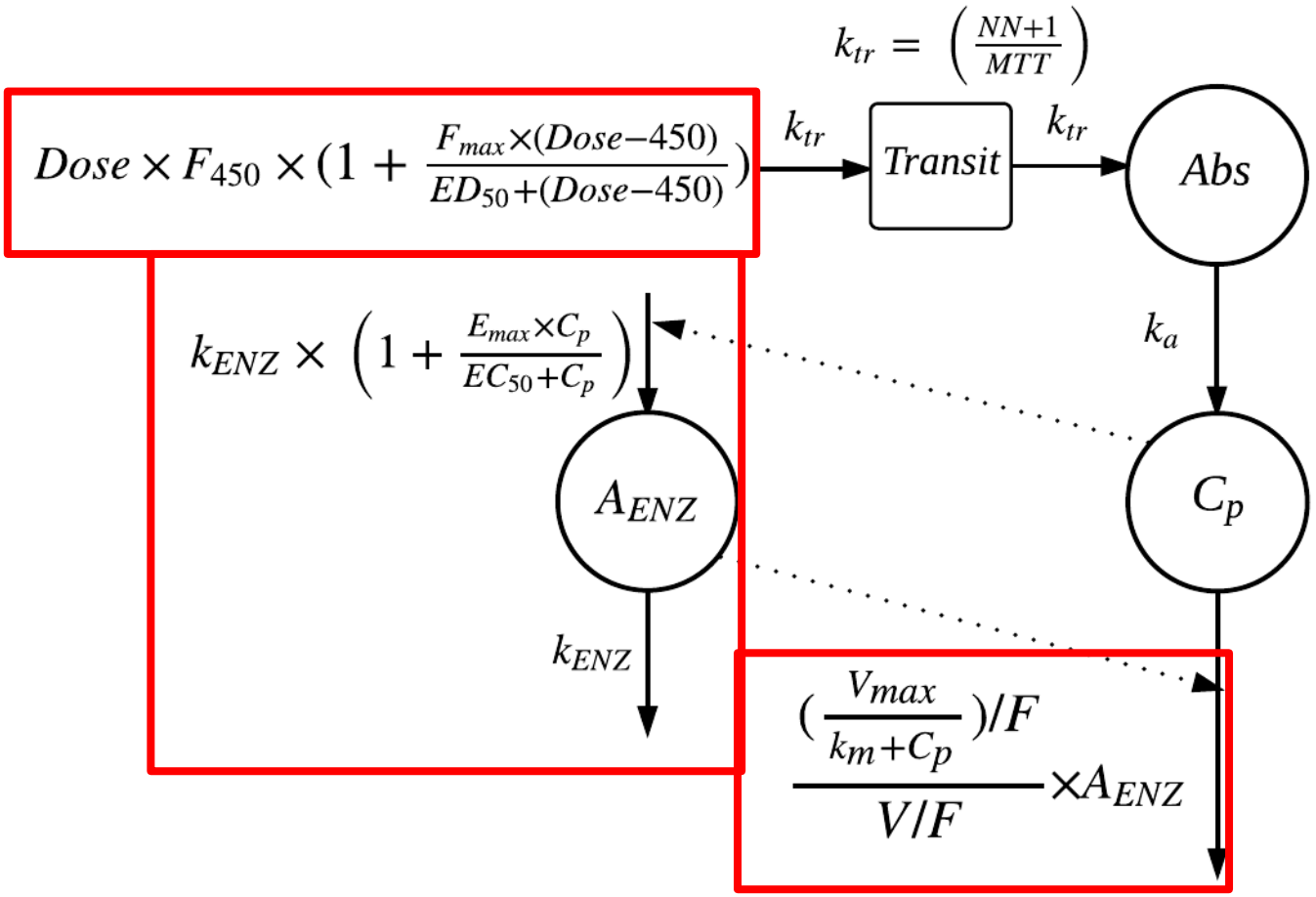
- Allometric scaling of CL/F and apparent volume of distribution (V/F)
  - Different models using fat free mass (FFM) or body weight
- Non-linear increase in exposure
  - For CL/F: Linear and Michaelis-Menten relationships between CL/F and rifampicin concentration
  - For F: Linear and E_{max} relationships between F and dose
- Variability in parameters
  - Inter-individual variability, inter-occasion variability, correlations

Final population PK model

- 1-compartment disposition
- V/F and CL/F scaled using FFM only
- Transit compartment model accounted for absorption
- Michaelis-Menten relationship between CL/F and rifampicin concentration
  - $\frac{CL}{F} = \frac{V_{max}}{C_p + k_m}$
- E_{max} relationship between F and dose
  - $F = F_{450} \times (1 + \frac{F_{max} \times (Dose - 450)}{ED_{50} + (Dose - 450)})$

C_p = rifampicin plasma concentraion

Final population PK model



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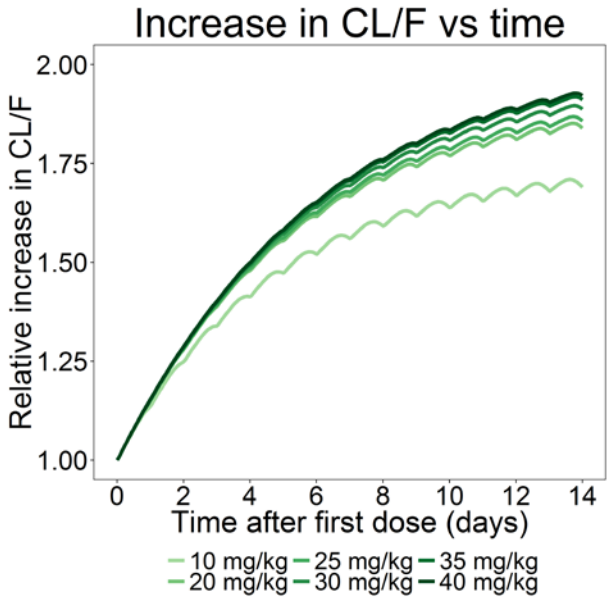
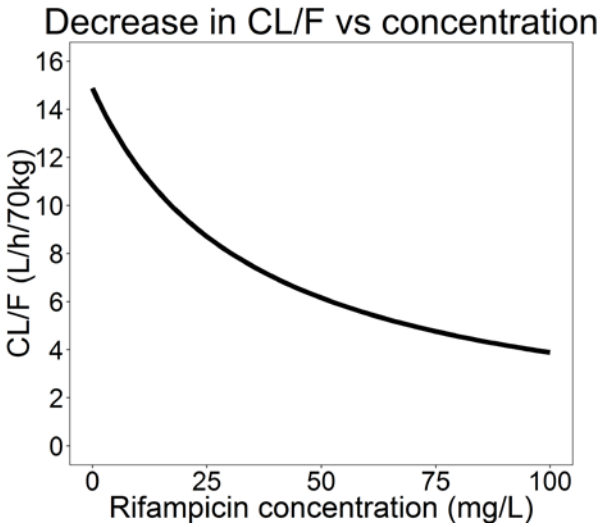
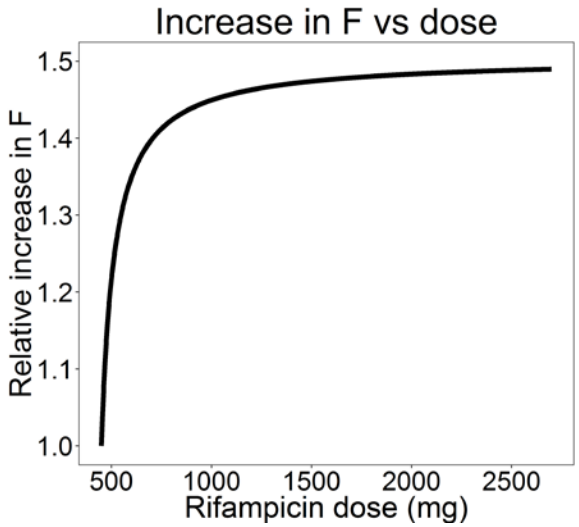
Predicted non-linear relationships

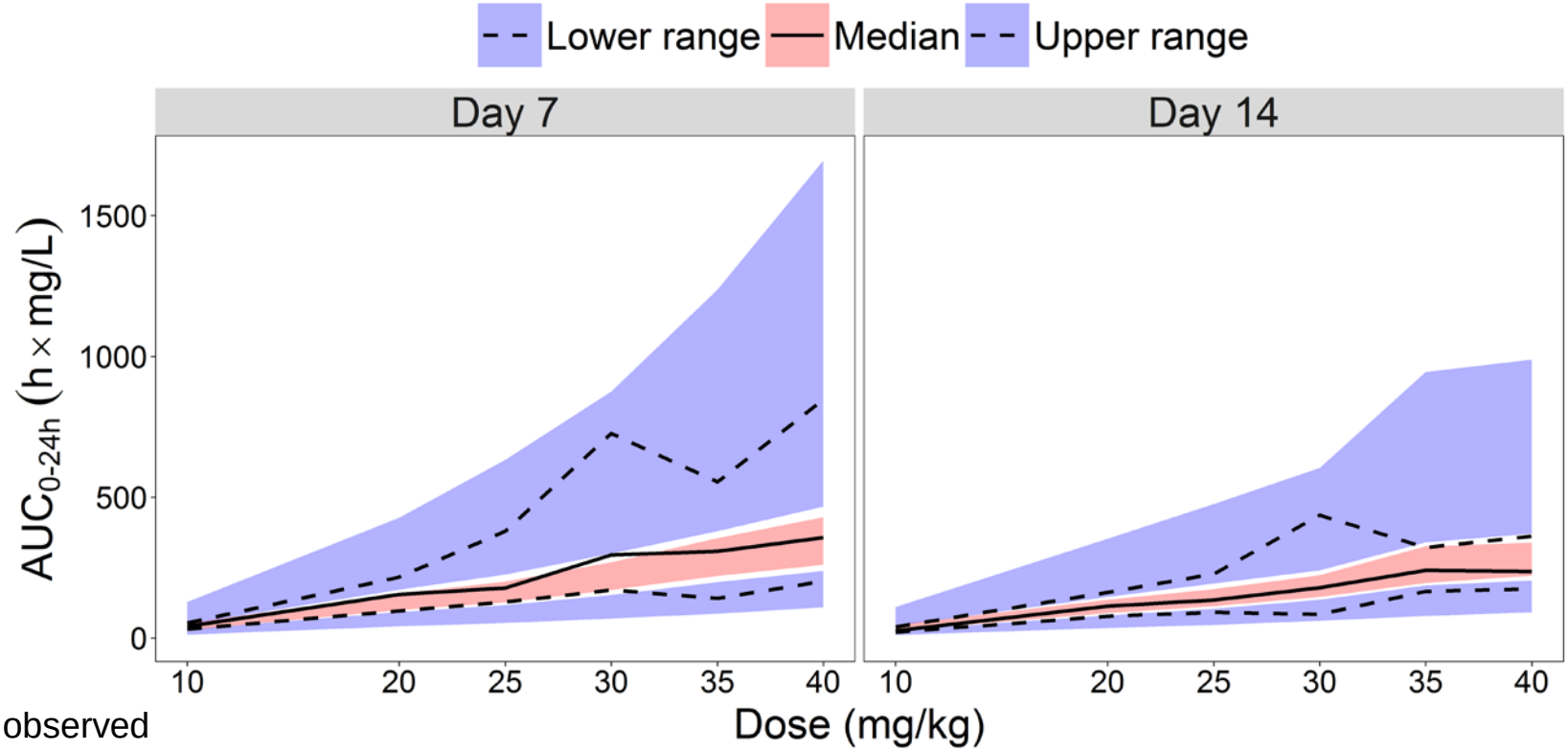






Rifampicin dose-exposure

Posterior predictive check of $AUC_{0\text{-}24h}$[1]



Lines = observed

Shaded ares = predicted

[1]Acharya *et al*. Comput Methods Programs Biomed 2016

Conclusions

- Rifampicin exposure in the studied dose range 10-40 mg/kg was successfully described
- The final model included multiple structural components to account for non-linearities
  - Dose-dependency in F (E_{max} relationship)
  - Concentration-dependency in CL/F (Michaelis-Menten)
  - Time-dependency in CL/F (enzyme turn-over model)
- This allows for clinical trial simulations and can be used to forecast exposures at the individual patient level, as useful for TDM

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