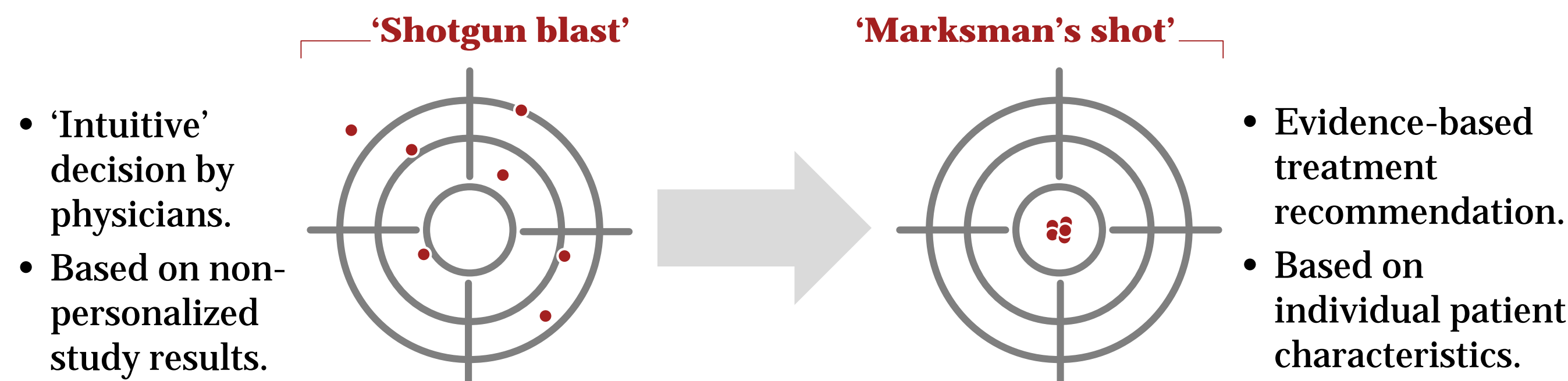


Model (PHREND®) for personalized prediction of treatment response in relapsing remitting multiple sclerosis (RRMS)

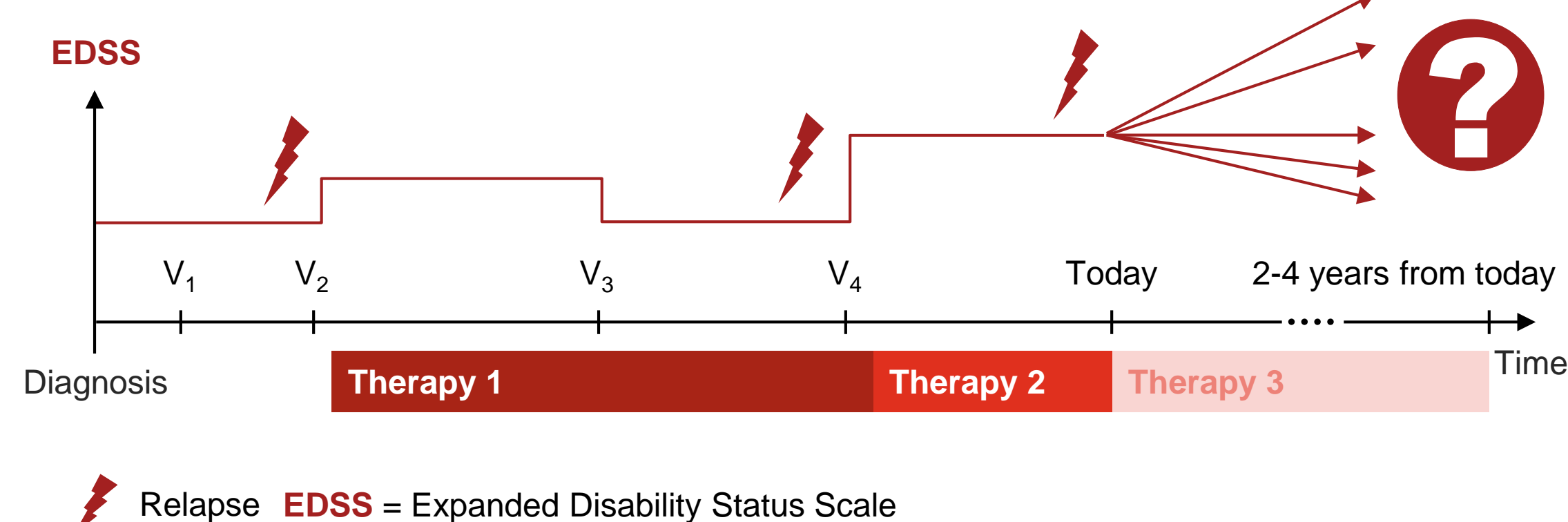
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Project goals

- In **multiple sclerosis (MS)**, treatment decision is currently based on **intuition from physicians**.
- “Trial and error” takes up time, is cost intensive and accelerates the disease progression.
- Patients have a desire to get a second opinion** on which treatment could work best for them based on the experience from similar patients.



Variables of interest



Indicators of treatment response

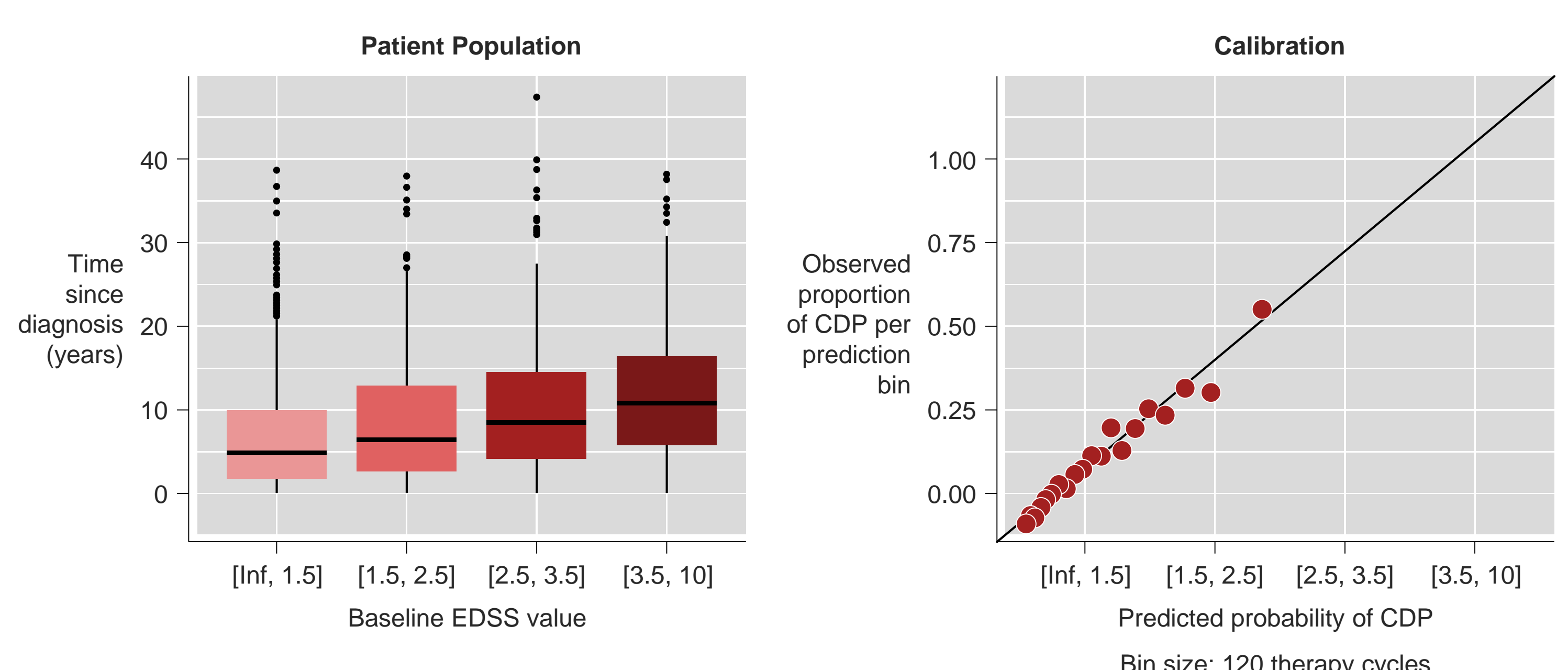
- Which treatment can reduce the **number of on-therapy relapses**?
- Which treatment can reduce the **probability of an on-therapy confirmed disease progression (CDP)** based on the EDSS value?

Modelling approach

- Predictive models** based on the assumption that:
 - the number of on-therapy relapses follows a **negative binomial distribution**;
 - the CDP follows a **binomial distribution**.
- Hierarchical generalized linear models (GLM)** are employed for both indicators of treatment response, with model parameters depending on patient's profile and treatment.
- The correlation between measurements coming from the same clinical site is incorporated through random effects.
- The duration of the therapy cycles is included as an offset term.
- Bayesian inference preferred due to the possibility of specifying (weakly informative) priors and preventing overfitting.

Model performance assessment

- Calibration:** how well do predictions compare to observations?
- Generalizability:** can the model be successfully applied to new data?
 - 10-fold cross-validation;
 - Leave-one-out cross-validation with respect to the clinical site;
 - Validation on test set.
- Comparison to **benchmark models** of decreasing complexity: is the knowledge of the patient's profile improving the predictions?
- Empirical test of the predicted treatment benefit: do patients profit from adhering to the recommendation?
- Robustness:** is the model sensitive to different choices of the priors, to the characteristics of the patient population and to the sample size?
- Quality of predictions assessed using the following statistical measures: mean squared error (MSE), log-likelihood, and Harrell's concordance statistic (C-Index).



Results and future prospects

Further developments

- Model refinement and extension (new variables and indicators of treatment response)
- Collection of new data
- Analysis of collected data on therapy decision

Status

- Currently in beta testing phase
- Roll out to German doctors' offices in 2018
- Results to be published in a scientific journal (in progress)
- Web-based App CE certified as medical device

Key success factors

- From doctors for doctors
- Use of RWE data
- Impact size
- Independence
- Living model
- Scalability to other diseases

Have a look at the PHREND® video:



Real-world evidence (RWE) data

- Since 2008 a Germany-wide network of physicians has maintained a database that currently documents more than 20'000 MS patients.
- The number of patients represents approx. 15% of the total market of MS patients in Germany (cf. Vfa 2014).

Patient ID	Age	Sex	Birth date	Date of diagnosis	EDSS value	Relapse (yes/no)	Factor n
1	56	M	26.11.1959	01.11.2004	2	yes	XXX
2	61	F	09.07.1954	26.06.2014	3	no	YYY
3	38	M	10.10.1977	06.04.2000	2.5	no	ZZZ
4	26	F	02.04.1969	13.05.2005	6	yes	QQQ

- The database contains **demographic data**, such as patient's age and gender, as well as **clinical data**, such as patient's quality of life, diagnosis, treatments, side effects, rationale for a change of treatment, and several others – over 1'000 variables in total.
- On average: >3 visits V_i per patient per year and 5 years observation period per patient.
- The database is active and with every half a year 500'000 entries are newly added.
- In total, more than 20'000 **therapy cycles**.

Business application

- Proposed solution: **Web-based App** providing personalized comparisons of treatment response using RWE data.
- Input from physician:** currently 12 easy-to-enter variables summarising the patient's profile.
- Options:** desired prediction period.
- Number crunching:** predictive model used to provide two indicators of treatment response for all disease modifying MS-treatments (if sufficient RWE data is available).
- Output:** probability of being relapse-/CDP-free + confidence interval for all available treatments.
- User friendliness:** model embedded in an enhanced tool to better guide the patient/physician communication and decision.

