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# Outline of an estimand proposal in progressive MS

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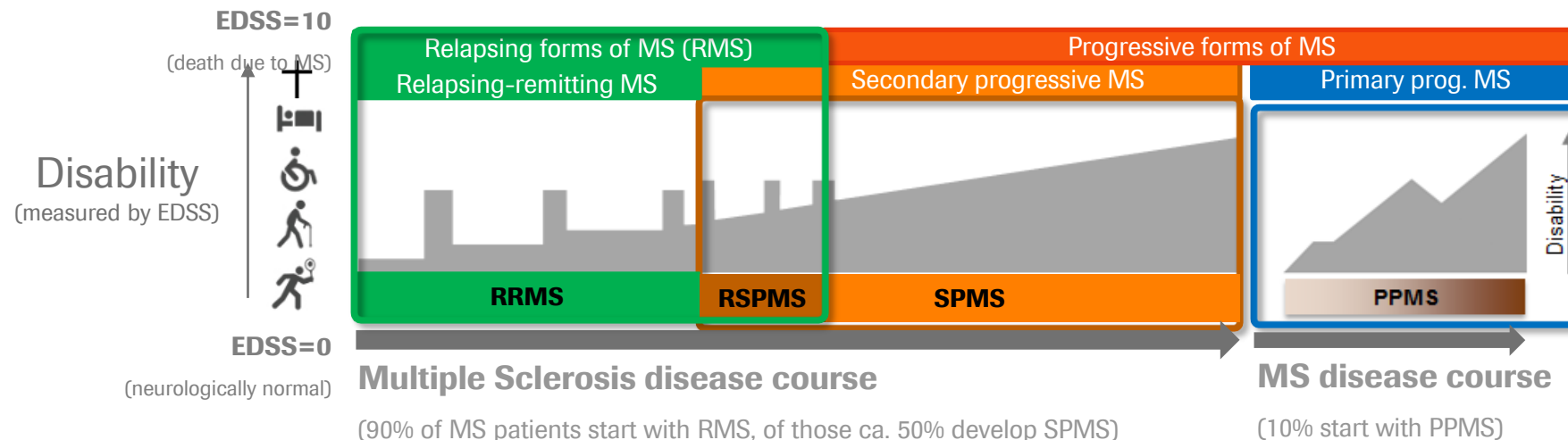


# Overview

- Introduction
- Study proposal
- Estimand framework
- Proposal for progressive MS
- Intervention effect of interest for relapse independent progression
- Summary

# Introduction on Multiple sclerosis

- Multiple sclerosis – a disease of the central nervous system
  - Autoimmune chronic demyelinating disease of the central nervous system (brain, spinal cord)
  - Characterized by inflammatory demyelinating events and eventually neuronal destruction
  - Most common neurological disorder in young adults: >1.5 mio people affected worldwide
  - Most common in Caucasians. RMS more common in females than males (2:1).



## Introduction on Multiple Sclerosis (cont.)

- Multiple Sclerosis (MS) is a progressing major disease
- Severity of MS is typically assessed using the *Expanded Disability Status Scale* (EDSS)
  - Ordinal rating system ranging from 0 (no neurological deficits) to 10 (death due to MS) in 0.5 step increments
  - Clinician-administered assessment scale
  - Progression defined as a worsening of 1 point or 0.5 points on the EDSS scale, required to be confirmed by a second assessment 3 months later
  - Time to confirmed disease progression is then defined as the time between randomization and the time of the first IDP which was subsequently confirmed
- Patients with progressive MS ultimately all progress by nature of the disease. However, *disease progression* needs to be differentiated from *relapses* which are clinically different and tend to be of short duration and allow patients to recover.

# Study frame work

- Think of a randomized double blind phase III study including for example 1000 patients
  - 1:1 randomization
  - Time to event design with follow up of all patients till the pre-specified number of events is reached
  - Events to be confirmed after three months in order to count
  - EDSS assessments performed in 3 months intervals
  - Chronic disease, hence patients treated for the duration of the study
- Occuring major intercurrent events
  - Missing confirmation assessment
  - Stopping therapy
  - Start of rescue therapy which can be effective today
- Intercurrent events can lead to corresponding missing data

# Estimand attributes

- **Treatment**  
Fixed dose, patients treated for whole duration of the study. At the end of the trial patients may start open label extension treatment
- **Population**  
Characterized by I/E criteria. Nothing MS specific
- **Variable**  
For MS this is time to confirmed disease progression based on EDSS assessment
- **Population-level summary**  
HR

# Intercurrent events (ICE)

- Differentiation between two categories of ICE
  - ICE between randomization and date of IDP
  - ICE between date of IDP and scheduled confirmation 3 months later.
- Difference between ICE and missing data
  - ICE can happen in real life outside study setting as well
  - Missing data are typical for study setting and occur only due to the study setting

# Intercurrent events (ICE)

- Treatment stop due to lack of efficacy
- Treatment stop, not efficacy related,
- Start of other DMT therapy, due to lack of efficacy,
- Start of other DMT therapy, not efficacy related
- Relapse event,
- Death



# Associated missing data events

- Drop-out before IDP (i.e. withdrawal from the study) for efficacy reasons
- Drop-out before IDP, not efficacy related,
- Missing confirmation assessment needed for CDP (if at 12 weeks or 24 weeks)
- Missing intermediate information in case of an IDP at the restart of assessment (all other cases of intermediate missingness is of no impact)

# Different strategies for handling ICE

- **Treatment policy strategy:** We ignore the intercurrent event for the definition of IDP (no event and continue to follow up) and use future data as observed (assuming no future missing data problem)
- **While on treatment strategy:** We ignore any intercurrent event and any information after end of treatment
- **Hypothetical strategy:** We try to estimate future outcome in case the intercurrent or missing data event would not have happened
- **Composite variable strategy:** We make the intercurrent or missing data event part of the primary endpoint event, i.e. CDP (composite endpoint)
- **Principal stratum strategy:** This is of interest to estimate the treatment effect in patients who have no relapse activity (non-relapsing SPMS or PPMS populations)

# General concept

- We need to define an estimand strategy for each ICE
- Missing data events following an ICE should follow the strategy of the ICE
- Example: ICE Treatment stop not efficacy related
  - We choose a treatment policy strategy for this ICE
  - Therefore, data still sampled after treatment stop not efficacy related, will still be used
  - As soon as afterwards a patients drops out of the study and not further information is available, the patient has still to be handled afterwards in the analysis according to this estimand

# Proposal for estimands for ICE in progressive MS

Intercurrent event	Estimand strategy	Comments
Treatment withdrawal for lack of efficacy	Composite variable or treatment policy strategy	Impute an event or use future information. Keep patients on study
Treatment withdrawal, not efficacy related	Treatment policy strategy	Use future information. Keep patients on study
Start of other DMT therapy due to lack of efficacy	Treatment policy strategy (until highly effective DMT would be available)	Since start of other DMT therapy also means treatment withdrawal
Start of other DMT therapy, not efficacy related	Treatment policy strategy (until highly effective DMT would be available)	Since start of other DMT therapy also means treatment withdrawal
Death	Composite variable strategy or ignore	Imputation of event. Since number of deaths usually balanced and low in size, simple censoring likely not changing anything (“ignore”)
Relapse event	<ul style="list-style-type: none"> <li>- Hypothetical strategy to estimate effect on progression independent of relapses</li> <li>- Principle stratum strategy to estimate treatment effect in non-relapsing patients</li> </ul>	

## Some remarks

- Sometimes the choice of an estimand strategy is not straightforward
- Example: Treatment withdrawal for lack of efficacy
  - Composite endpoint accepts that treatment withdrawal related to worsening of the disease but it also means ignoring future potentially still available information perhaps not indicating an event (which may be possibly due to use of rescue therapy)
  - Treatment policy strategy can use further available information but can also lead to informative censoring
- Time to event setting allows composite variable strategy easily but pose interpretation questions
- Death does not play a major role as it is not frequent in studies. Clinicians tend to ignore it for the endpoint of time to CDP
- Relapse event is interesting as it can happen any time but is rather rare in PPMS and more frequent in SPMS.

# Relapse independent progression

- Either go into a PPMS population where relapses are more rare and can be rather ignored or look for relapse independent confirmed progression
- General choices

Intercurrent event	Estimand strategy	Comments
Events as for CDP	Events as for CDP	Events as for CDP
Relapse event	Principal Stratum strategy*	Use of Bayesian statistics to adjust for the unknown relapse free stratum or other techniques for the analysis

\*Magnusson BP, Schmidli H, Rouyrre N, Scharfstein DO (2019) Bayesian inference for a principal stratum estimand to assess the treatment effect in a subgroup characterized by postrandomization event occurrence. *Statistics in Medicine*, doi: 10.1002/sim.8333

# Summary

- The right choice of the estimand is important for MS
- Missing data events following an ICE should follow the estimand strategy for the ICE. This may pose questions on imputation of future events
- We need to drive for simplicity. With too many ICE and using different estimands this can pose significant problems in the implementation
- Important is to make efforts through population selection and inclusion/exclusion criteria to reduce the number of patients having ICE and minimize interpretation issues
- Given the time to event setting for the primary endpoint composite variable strategy are rather easy to implement but may pose interpretation hurdles
- Relapse independent CDP is a great example for the use of a principal stratum strategy. Estimation of the patients with relapse independent progression in the control may however pose a significant problem

# Backup Slides



# Proposal for handling missing data events

Missing data event	Action
Study withdrawal after treatment withdrawal before IDP due to lack of efficacy	<ul style="list-style-type: none"> <li>- Composite variable strategy: Cannot happen anymore, follow-up irrelevant</li> <li>- Treatment policy strategy: Multiple imputation based on                             <ul style="list-style-type: none"> <li>○ Observed progression rates in placebo and active treatment patients who stop therapy due to lack of efficacy and stay on study after treatment withdrawal</li> <li>○ Placebo response based imputation of missing data</li> </ul> </li> </ul>
Study withdrawal after treatment withdrawal before IDP due to other reasons	Treatment policy strategy: Multiple imputation based on placebo response based imputation of missing data
Missing IDP confirmation	<ul style="list-style-type: none"> <li>• Imputation of an event</li> <li>• Multiple imputation based on observed confirmation rates in placebo and active treatment patients who experience and IDP as sensitivity analysis</li> </ul>
Missing intermediate information	Ignore event, Take time of CDP when observed

# Bayesian framework to predict the missing stratum membership

- Assumptions to be made
  - Monotonicity assumption that a patient who would not have relapsed if untreated (receiving placebo) would not experience a relapse if assigned to the experimental treatment arm.
  - Assumptions about missing data and covariates as not all patients had available data for the period of time being considered due to variable follow-up time. Specifically, it needs to be assumed that
    - Principal stratum membership is independent of missingness conditional on the covariates; and
    - Disability is independent of missingness conditional on stratum membership, covariates and treatment.
  - Assumptions of probabilistic model that captures the data-generating distributions and prior distributions for each parameter for the Bayesian analyses.
- Extensive sensitivity analyses needed to evaluate impact of untestable assumptions and deviation from those assumptions.