Construction of an Estimand in a Clinical Trial on Progressive Multiple Sclerosis

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Multiple sclerosis (MS)

- Inflammatory and degenerative disease of human central nervous system (CNS).
- Affects around **2.5 million people worldwide**.
- One of most common neurological disorders and causes of disability of young adults, especially in Europe and North America.
- Symptoms include:
  - weakness,
  - pain,
  - visual loss,
  - bowel / bladder dysfunction,
  - cognitive dysfunction.

Diagnosis and phenotypes

- Structured diagnostic criteria that rely on
  - clinical observation,
  - neurological examination,
  - brain and spinal cord MRI scans,
  - measurement of electrical activity of the brain in response to stimulus,
  - examination of cerebrospinal fluid.
- Three phenotypes: distinguished by occurrence and timing of relapses relative to disease onset and disability progression:
  - Relapsing remitting MS (RRMS),
  - primary progressive MS (PPMS),
  - secondary progressive MS (SPMS).

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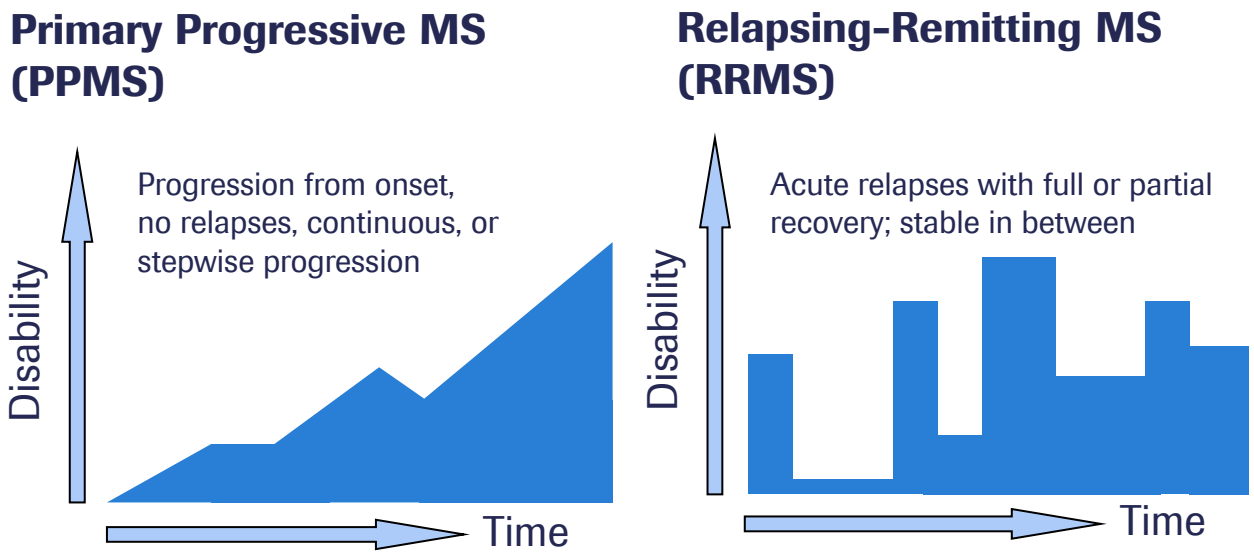
PPMS vs. RRMS

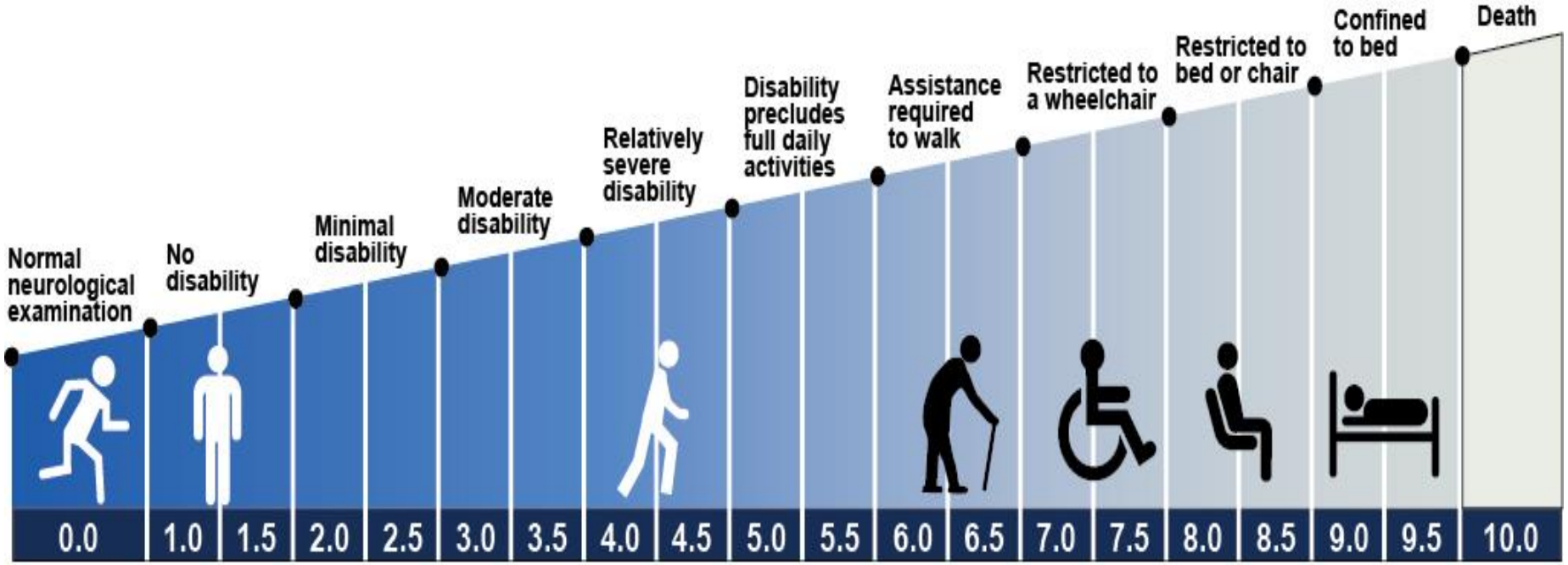


- **Relapses**: these are
  - clinically different,
  - of short duration,
  - and transient.

Clinical measure of disability: EDSS

Kurtzke Expanded Disability Status Scale

- EDSS standardly used to identify progression and relapses in MS.
- **Clinically meaningful** increase:
  - 1 point if baseline EDSS ≤ 5.5,
  - 0.5 points if baseline EDSS > 5.5.



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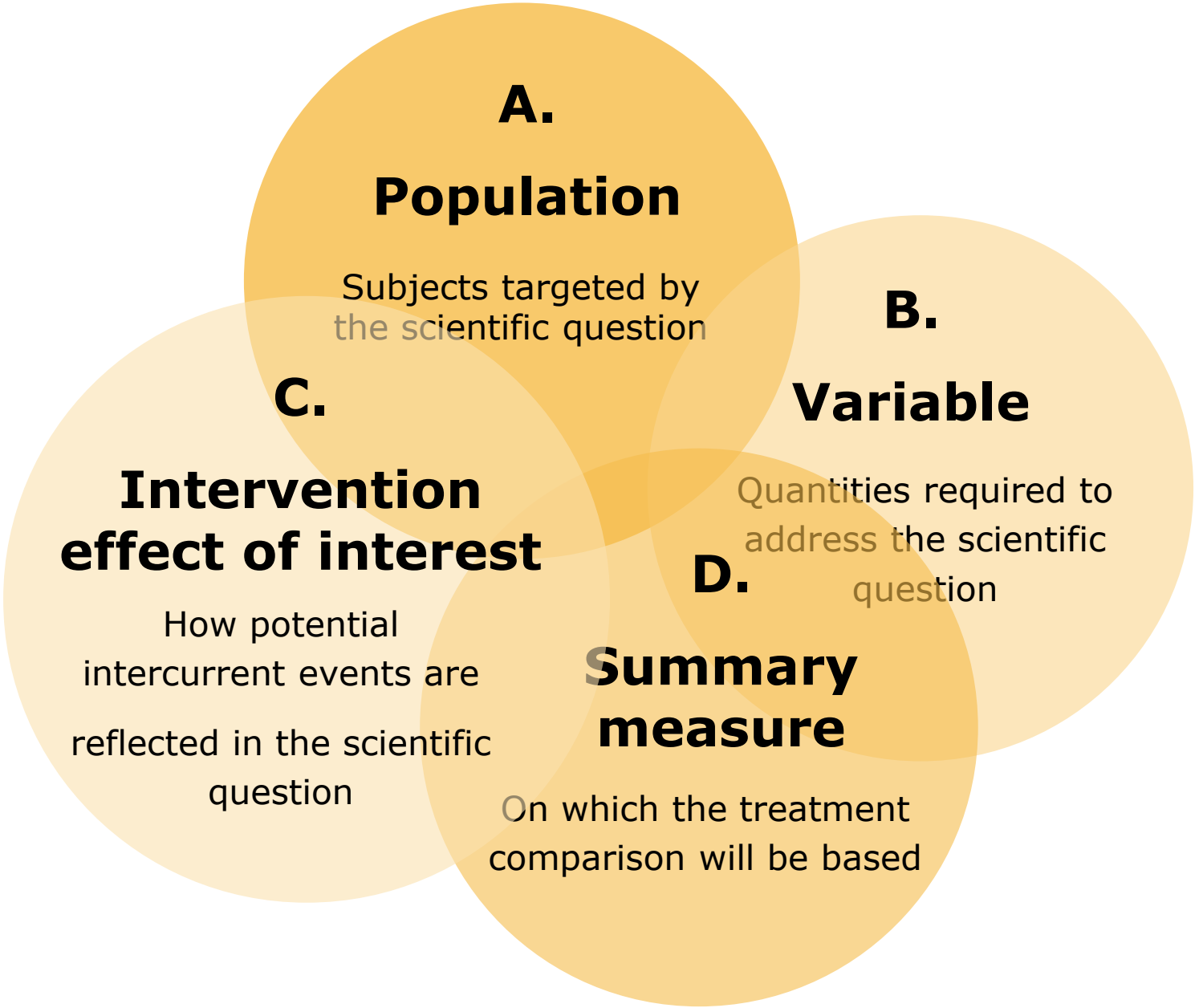
Clinically relevant endpoint

- Time to onset of **confirmed** disability progression:
  - initial progression assessment (IDP, see previous slide),
  - sustained for at least 12 weeks, based on **scheduled** visits.
- Why **confirmed**?
  - PPMS and RRMS ultimately all progress, by nature of disease.
  - But: progression needs to be differentiated from relapse.
  - Confirmation robustifies endpoint against variability in EDSS assessment.
  - Literature: in PPMS about 80% confirmation of IDPs.
- Why **scheduled**?
  - Patients experience «ups» and «downs» in the course of their disease.
  - «Downs» → more frequent, «ups» → less frequent assessments.
  - Avoid assessment bias between arms.

Time to onset of confirmed disability progression



Time to onset of confirmed disability progression

1. **Population**: defined through list of in- and exclusion criteria, nothing specific to MS.

2. **Variable**: Time to onset of confirmed disability progression, defined through
   - starting date: date of randomization,
   - event date: date of IDP, if confirmed.

3. **Intervention effect of interest**:
   - Intercurrent events between randomization and IDP.
   - Intercurrent events between IDP and confirmation (actually tied to variable).

4. **Summary measure**: hazard ratio.

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Background on exemplary trial

- Some of the following considerations inspired by RCTs in the field:
  - Against placebo.
  - Double-blind.
- **Lifelong** treatment (or until withdrawal from study).
- EDSS assessed in **12 weekly** intervals.
- Discontinuation of treatment: patients goes to safety follow-up, EDSS still collected.
- Withdrawal from study: no EDSS collected anymore.
- Death: in this population, patients
  - neither expected to die from MS nor
  - due to either treatment.
- More withdrawals expected during planning, observed rates higher than assumed in sample size computations.

Randomization → IDP

Intercurrent event	Action	Date	Estimand strategy
Discontinuation of treatment	Censored	Last EDSS assessment during treatment	While on treatment
Loss to follow-up	Censored	Last EDSS assessment during treatment	While on treatment
Withdrawal from study	*Censored*	*Last EDSS assessment during treatment*	*While on treatment*
Death	*Censored*	*Last EDSS assessment during treatment*	*While on treatment*

- Withdrawal, death: not explicitly pre-specified, treated as discontinuation of treatment.
- Observed withdrawal pattern (trial overall): 34% in placebo, 21% in treatment arm → censoring potentially informative.

IDP → confirmation

Clinical event		Action	Date	Comment
Scheduled confirmation ≥ 12 weeks after IDP		Event	IDP	
No scheduled confirmation after IDP	remains on treatment	Censored	Last EDSS assessment	
	discontinuation of treatment	Event («imputed events»)	IDP	80% confirmation rate according to literature
	loss to follow-up			
	withdrawal from study			
	death			

- Observed withdrawal pattern between IDP and confirmation (available after unblinding only!):
  - Placebo **5%**,
  - treatment **2%**.
- «Imputation» of events conservative? **Yes** (not getting withdrawals means event) and **no** (higher withdrawal rate in placebo!).

Conclusions

- We apply estimand framework to existing MS endpoint **post-hoc**, to understand how framework will help in future studies.
- If estimand framework had existed at the time – would have facilitated
  - identification and classification of intercurrent events already during protocol development,
  - would likely have helped discussion with clinicians and regulatory colleagues.
- Special feature: intercurrent events between
  - randomization and IDP and
  - IDP and confirmation.
- Definitions depend on indication: Discontinuation of treatment after IDP =
  - event for PPMS (~80% confirmation rate),
  - but censored for RRMS (~30% confirmation rate).
- Maybe informative censoring? Account for in future trials via IPCW → hypothetial estimand?

Doing now what patients need next