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Use Case Multiple Sclerosis (UC MS): The many challanges to construct a treatment decision rule

Ulrich Mansmann,
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Alexander Wuschek, Joachim Havla, Markus Krumbholz, Antonios Bayas,
Alexander Hapfelmeier, Irmak Ön Seker, Verena Hoffmann, Marlien Hagedorn

and the DIFUTURE Consortium

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Overview

- Data and endpoints - surrogacy
- Decision Support versus Decision Rule: Process vs single prediction algorithm
- Decision rules from observational data
- Causal issues
- Unobserved confounding
- Validation: Patient relevant endpoints

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Definitions

- Treatment Decision Support: Tools and processes used to enhance (empower) patient‘s healthcare decision-making.
- Clinical Decision support: Addressing medical professionals

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Which treatment is best for a newly diagnosed MS patient?

- Watch and wait (WW)
- Moderately Effective Therapies (MET)
- Highly Effective Therapies (HET)

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Data base for decision making on newly diagnosed MS patients

Laboratory results: about **100 additional measurements** per patient, including laboratory data from cerebrospinal Fluid (CSF).

Diagnoses: information on the course and development of MS, relevant comorbidities and adverse reactions.

Medication: data on MS-specific medication (treatment time, course, type).

MS-specific clinical documentation: **(~100 attributes)** includes data on case history, initial manifestation of the disease, episodes and symptoms as well as electrophysiological parameters (evoked potentials).

Clinical scores: **five different scores**, including EDSS, per patient as well as the individual parameters used to calculate the clinical scores (~100 attributes).

MRI-derived parameters: about **50 attributes** describing MRI scans (e.g., lesion load) originating from automated image analyses and structured radiology reports.

Patient-Reported Outcomes: includes about **50 attributes**.

Biosamples & omics: integration of two extension modules of the national core dataset.

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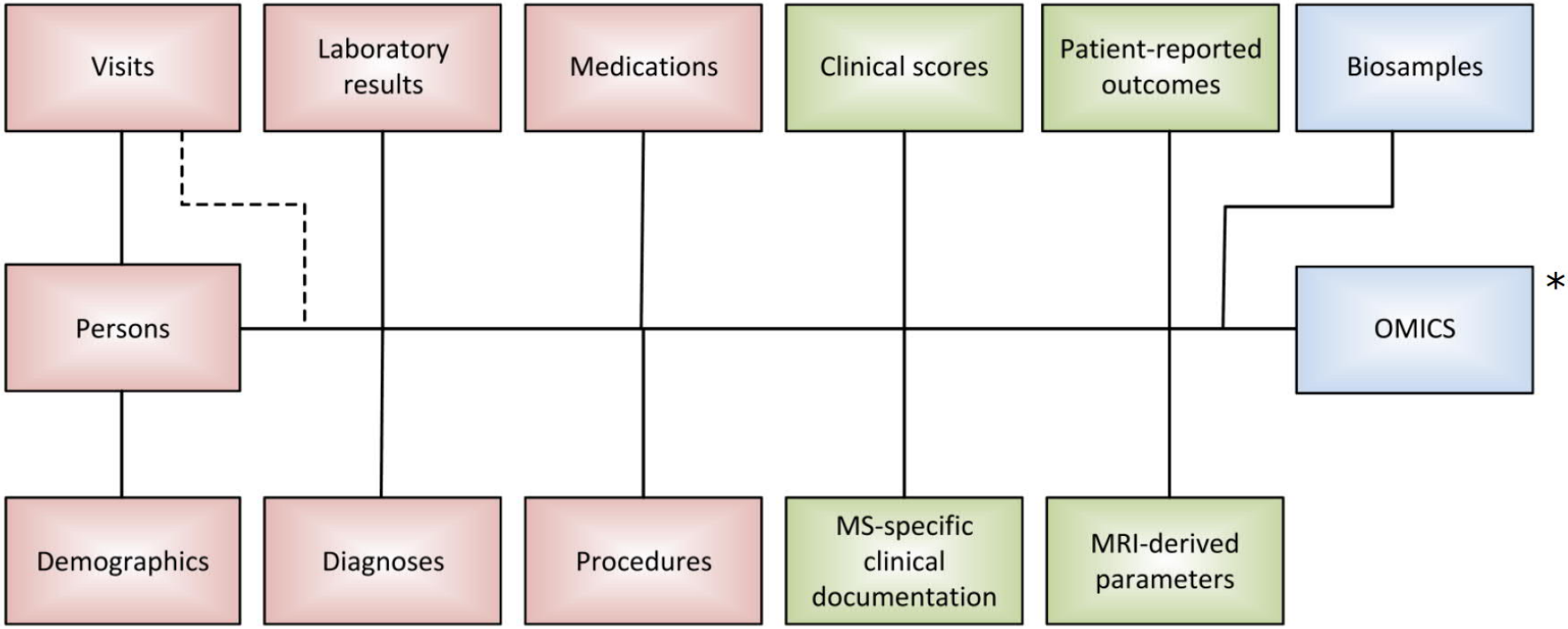
Core Data Set for clinical practice



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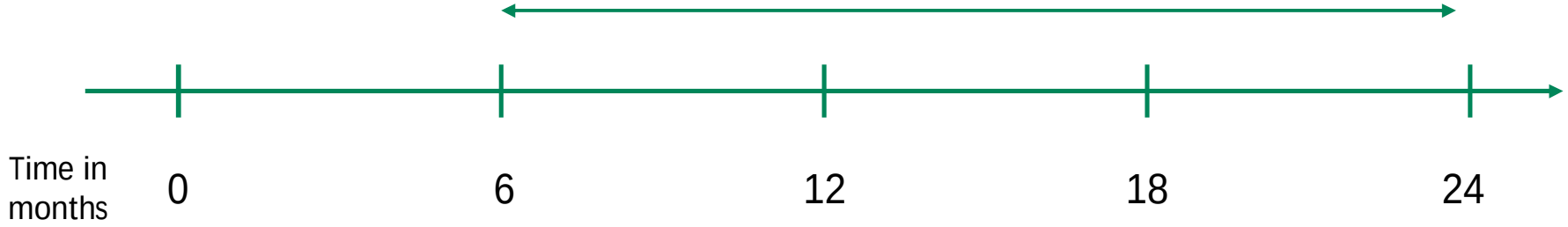
Efficacy endpoint

MRI based success criterion:
No new lesion and no increase of lesions by more than 20%



Surrogacy issue with EDSS or other functional scores.

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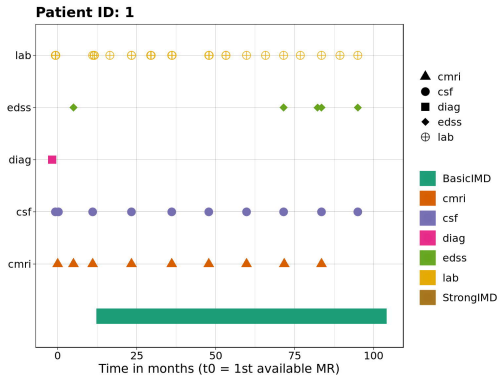

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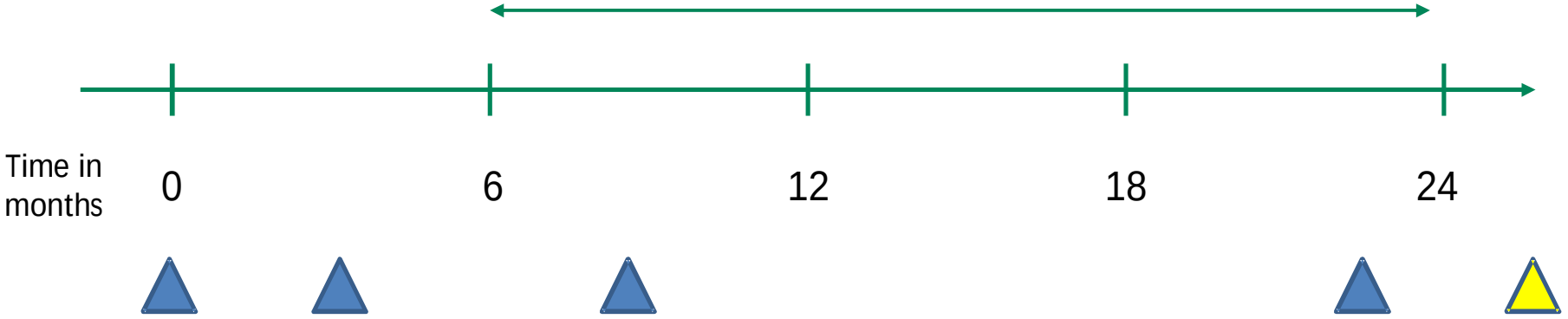

When does the event happen?
Interval censored event data
Hazards regression model (proportional hazards / additive hazards)?

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A Formal Decision Rule

- We plan to calculate three success probabilities: one for each of the three treatment option (WW, MET, HET) depending on individual features:

$$P(\text{Success} \mid \text{Treatment, relevant individual patient data}) =$$
$$P(S+ \mid T, X) =$$
$$\text{Probability of no event taking place up to month 24}$$

  and take the treatment with the highest success probability.

- These probabilities may be the input for a more complex decision making process also considering expected complications, harms.

- Here we concentrate on issues related to the derivation of the predictive probability.

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Algorithms for estimation of treatment predictive success probabilities

To help the reader navigate through the thick forest of emerging subgroup identification methods, we propose a check list of several important features that should be examined for any prospective method. These features are defined as follows:

(1) modeling type: Freq (Frequentist), Bayes (Bayesian); P (parametric), SP (semiparametric), NP (nonparametric);
(2) dimensionality of the covariate space: low, medium, high;
(3) results produced by the method: B (selected biomarkers or biomarker ranking based on VI scores that can be used for tailoring), P (predictive scores for individual treatment effects), T (optimal treatment assignment), S (identified subgroups);
(4) evaluation of the Type I error rate/false discovery rate for the entire subgroup search strategy: yes, no;
(5) application of complexity control to prevent data overfitting: yes, no;
(6) control (reduction) of selection bias when evaluating candidate subgroups: yes, no;
(7) Availability of 'honest' estimates of treatment effects in identified subgroups: yes, no; and
(8) availability of software implementation: C (R package available on the CRAN web site), B (R code available on the biopharmaceutical network web site), P (proprietary).

Statistics in Medicine
Tutorial in Biostatistics
Received 4 August 2015, Accepted 5 July 2016 Published online 3 August 2016 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/sim.7064

Tutorial in biostatistics: data-driven subgroup identification and analysis in clinical trials

Ilya Lipkovich,[a*†] Alex Dmitrienko[b] and Ralph B. D'Agostino Sr.[c]

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Big-data Clinical Trial Column

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Subgroup identification in clinical trials: an overview of available methods and their implementations with R

Zhongheng Zhang[1], Heidi Seibold[2], Mario V. Vettore[3], Woo-Jung Song[4], Vieille François[5]

Algorithms for estimation of treatment predictive success probabilities

Table 1 Comparisons of different methods for subgroup identification

Methods	Philosophy	Advantages	Limitations
Conventional regression model	Truth is known/hypotheses are clear	Easy to understand for subject-matter audience	Needs hypothesis on interaction terms; higher-order interaction effects may be missed
Panelized regression model	Effects and treatment covariate interactions are linear or nonlinearities are known	Able to search a large number of covariate/interaction space; the model is easy to understand	Technically difficult to perform, needs sophisticated computation; the selection of penalty value (Lambda) is difficult; high order terms, if exist, is hard to interpret
Model-based recursive partitioning	Patients can be classified into subgroups where within the subgroups the model parameters (intercept and treatment effect) and between the subgroups at least one parameter is different. Effect sizes matter	Straightforward interpretation; effect size in subgroups can be illustrated; more interpretable than high-order interactions	Instability of tree structure; validity of parameter confidence interval is questionable (9,17)
QUINT method	Patients can be classified into subgroups with treatment effects going in different directions. Effect sizes don't matter.	Report qualitative treatment-subgroup interaction; Suitable for situations when the optimal treatment assignment is the primary focus; stepwise greedy search of covariates	Vulnerable to false positive and negative results; no treatment effect estimates
Adapted support vector machine classifier	Heterogeneous treatment effect is estimated as a variable selection problem	Able to account for the fact that predictive effects (treatment effect modifier) are weaker than prognostic effects; treatment effect for each subject can be estimated	Subject to false positive and negative results
Virtual twins method	Random forest ensemble to predict the probability of the outcome of interest for each subject in a counterfactual framework	Counterfactual framework that treatment effect for each subject can be estimated	Tendency to identify a false subgroup

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Algorithm for estimation of treatment predictive success probabilities

We use an Aalen model and assume (Aalen, 1978, 1989; Lin and Ying, 1994) for the hazard:

$$\lambda(t \mid T, X) = \lambda_0(t) + \beta_1 \cdot T + \beta_2 \cdot X + \beta_3 \cdot T \cdot X$$

$$P(S+ \mid T, X) = P(Y > 24 \mid T, X) = \exp\{ -\int_0^{24} \lambda(t|T, X)dt\}$$

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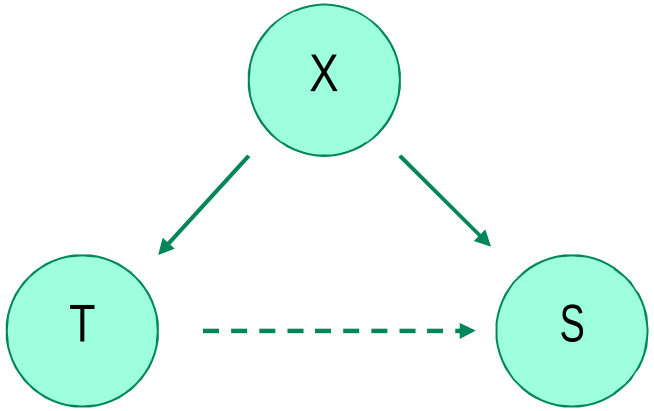
Unbiased Estimates – Causal Estimates
Inverse Treatment Probability Weighting



1.) Weight each observation by P(T|X)
2.) Apply algorithms for the estimation of individual success probabilities

Or

Adjust for confounding in the corresponding regression model

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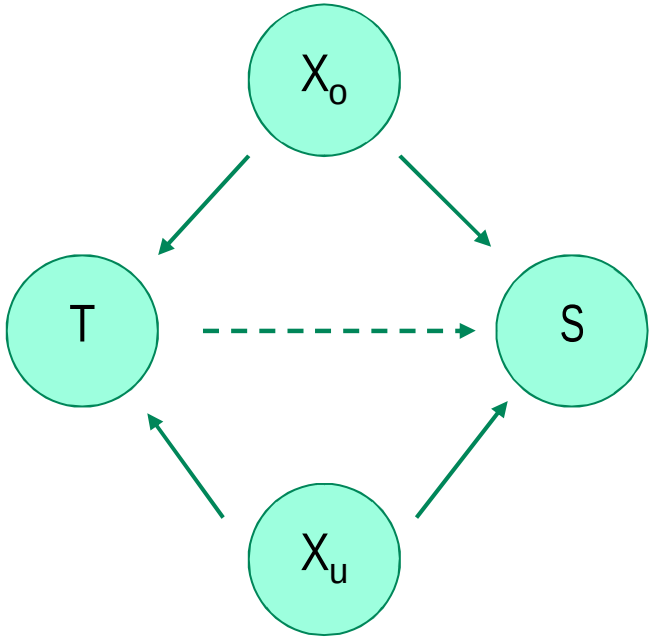
Unbiased Estimates – Causal Estimates



The individual patient features X consist on observed and unobserved parts: $X = (X_o, X_u)$

$P(S+ \mid T, X_o, X_u)$

It may not be wise to neglect the unobserved part, potential source of bias.

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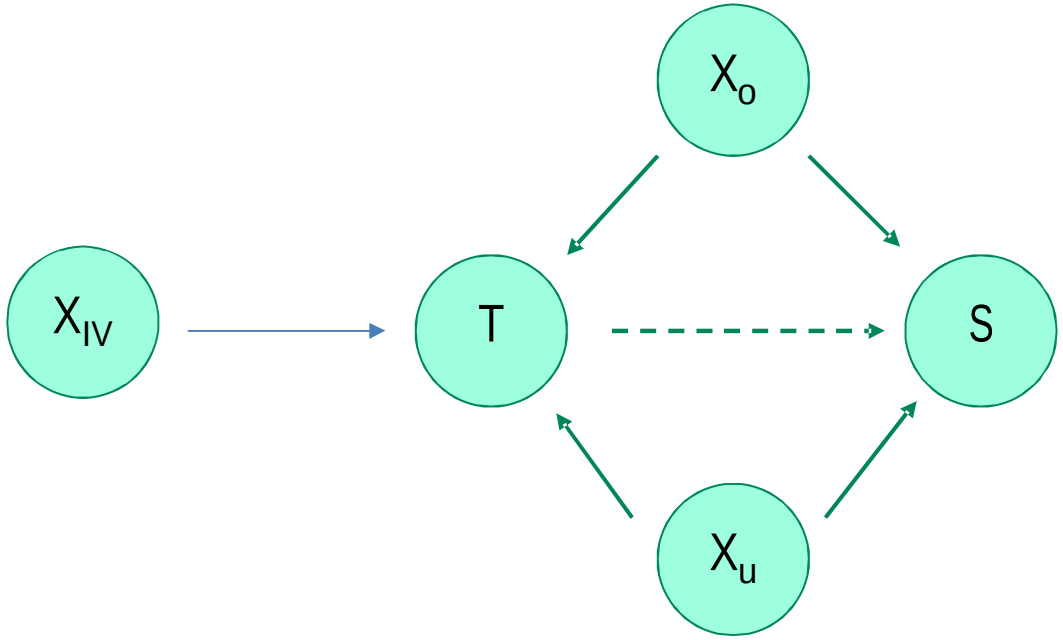
Instrumental variable set up



X_{IV} is the instrument variable:

1) X_{IV} is associated with T,

2) X_{IV} doesn‘t affect S except through its effect on T

3) X_u and X_{IV} do not share causes

Example for a possible IV: the doctor

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Applying the IV setup and two-stage residual inclusion

We would like to replace X_u by something which is observable:

Note that:

- X_u is independent of X_{IV}
- $\Delta = T - E[T|X_{IV}, X_o]$ is independent of X_{IV}
- If we are willing to assume that $X_u = \rho_0\Delta + \varepsilon$, where ε is an independent error term (Tchetgen et al., 2015), then we can handle the unobserved confounding.
- Δ is unknown but we can 'estimate' it using the residual.

Tchetgen Tchetgen EJ, Walter S, Vansteelandt S, Martinussen T, Glymour M. Instrumental variable estimation in a survival context. (2015). Epidemiology. 26(3):402-410. PMCID: PMC4387894.

This is a concept – independent of the algorithms used to calculate the residuals!

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Implementation into clinical work-up

International Journal of Colorectal Disease
October 2017, Volume 32, Issue 10, pp 1385–1397 | Cite as

The DGAV risk calculator: development and validation of statistical models for a web-based instrument predicting complications of colorectal cancer surgery

Authors | Authors and affiliations

Alexander Crispin, Carsten Klinger, Anna Rieger, Brigitte Strahwald, Kai Lehmann, Heinz-Johannes Buhr, Ulrich Mansmann

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Validation

Technical endpoints:

Treatment given + patient‘s feature → Score value
ROC curve using score values and real clinical success: Score should be low if no success and high given success under the treatment administered.

Patient relevant endpoints

Longer time with good functionality,
less complications or ADRs (adverse drug reactions)
Mostly assessed by a form of a RCT: Patients will be randomized on „using decision support“ versus „no decision support“

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Validation

Moja, L; Kwag, KH; Lytras, T; Bertizzolo, L; Brandt, L; Pecoraro, V; Rigon, G; Vaona, A; Ruggiero, F; Mangia, M; Iorio, A; Kunnamo, I; Bonovas, S (2014). Effectiveness of computerized decision support systems linked to electronic health records: a systematic review and meta-analysis. American Journal of Public Health. 104 (12): e12–22.

- Twenty-eight RCTs were included.
- CDSS use did not affect mortality (16 trials, 37395 patients; 2282 deaths; risk ratio [RR] = 0.96; 95% confidence interval [0.85, 1.08]).
- A statistically significant effect was evident in the prevention of morbidity, any disease (9 RCTs; 13868 patients; RR = 0.82; 95% CI [0.68, 0.99])

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Garg AX, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, et al. (2005). Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA. 293 (10): 1223–38.

Many CDSSs improve practitioner performance. To date, the effects on patient outcomes remain understudied and, when studied, inconsistent.

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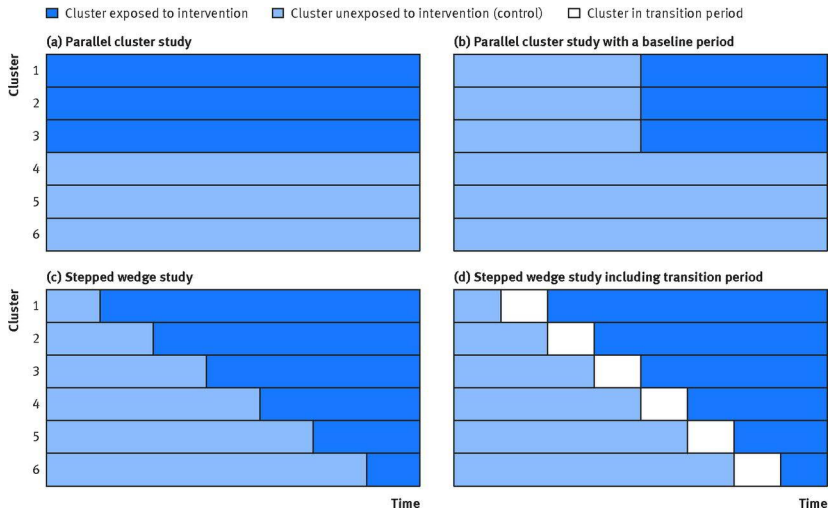
Validation

Randomized controlled trials:

- Classical RCT
- Cluster randomized trials
- Stepped-wedge trial



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Summary

Major challenges:

- Constructing a CDSS
  - Representative dataset
  - Endpoint, Surrogacy
  - Algorithm
- Confounding in observational data – causal strategies
- Implementation issues for clinical work-up
- Validating a CDSS – technical aspects versus patient related outcomes
- Transportability

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Thank you!