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Item Response Models for Translation in CNS disorders

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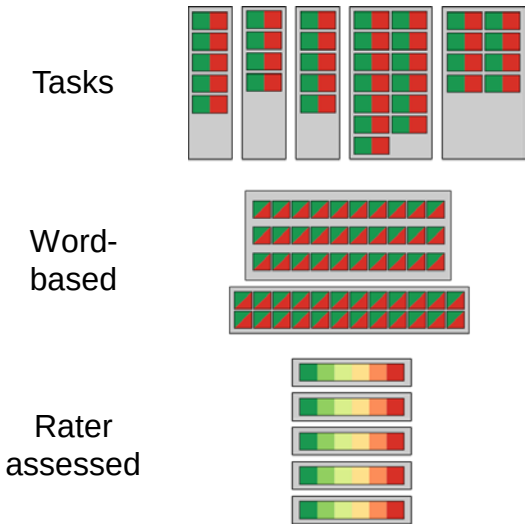
Composite endpoints

Alzheimer's Disease

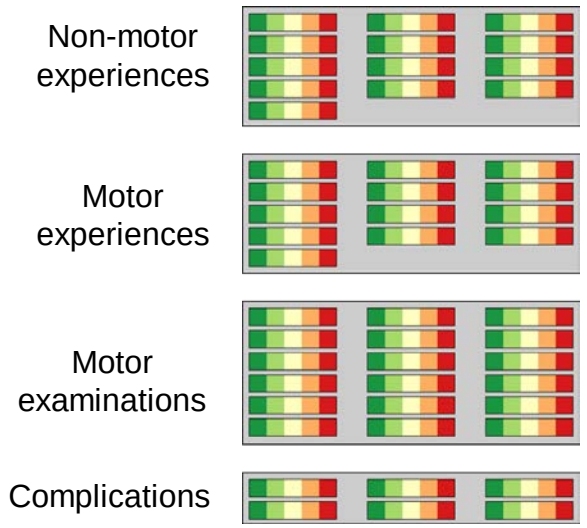
Alzheimer's Disease Assessment Scale - Cognition (ADAS-Cog)



Sum

Parkinson's Disease

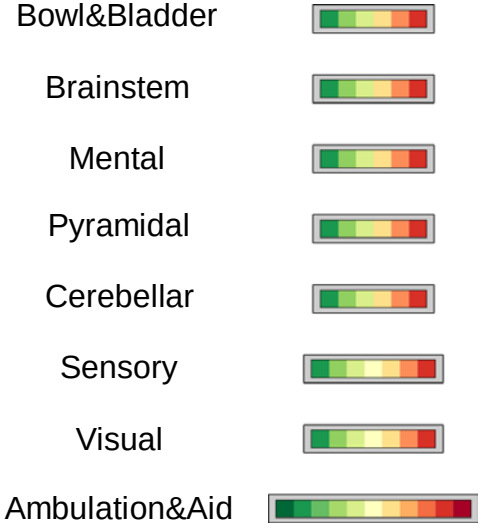
Movement Disorder Society - Unified Parkinson's disease rating scale (MDS-UPDRS)



Sum

Multiple Sclerosis

Kurtzke Expanded Disability Status Scale (EDSS)



Decision Tree

Models describe change in composite endpoints over time

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Composite endpoints & pharmacometric modeling

Alzheimer's Disease	Parkinson's Disease	Multiple Sclerosis
Alzheimer's Disease Assessment Scale - Cognition (ADAS-Cog)	Movement Disorder Society - Unified Parkinson's disease rating scale (MDS-UPDRS)	Kurtzke Expanded Disability Status Scale (EDSS)
Assessment	Assessment	Assessment

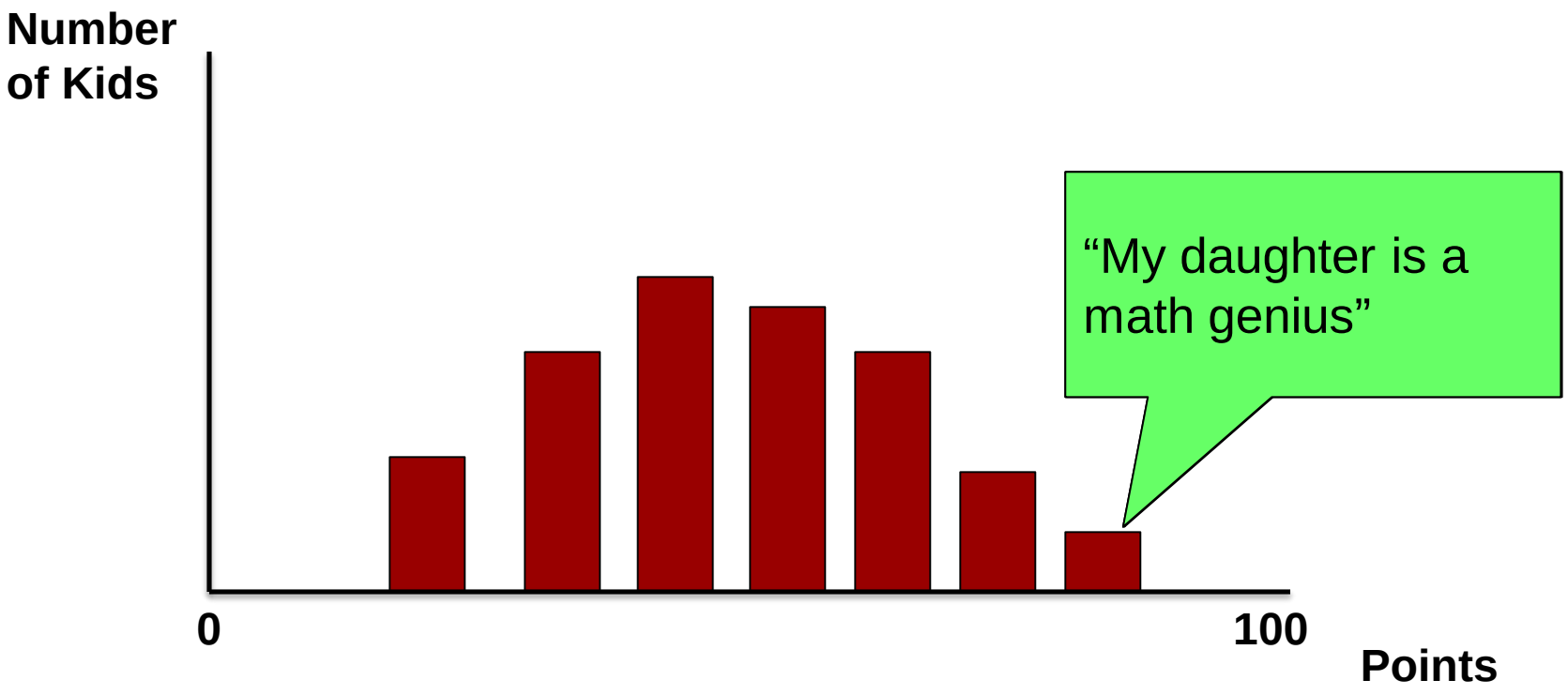
Standard analysis based on total score

Why use Item Response Models?

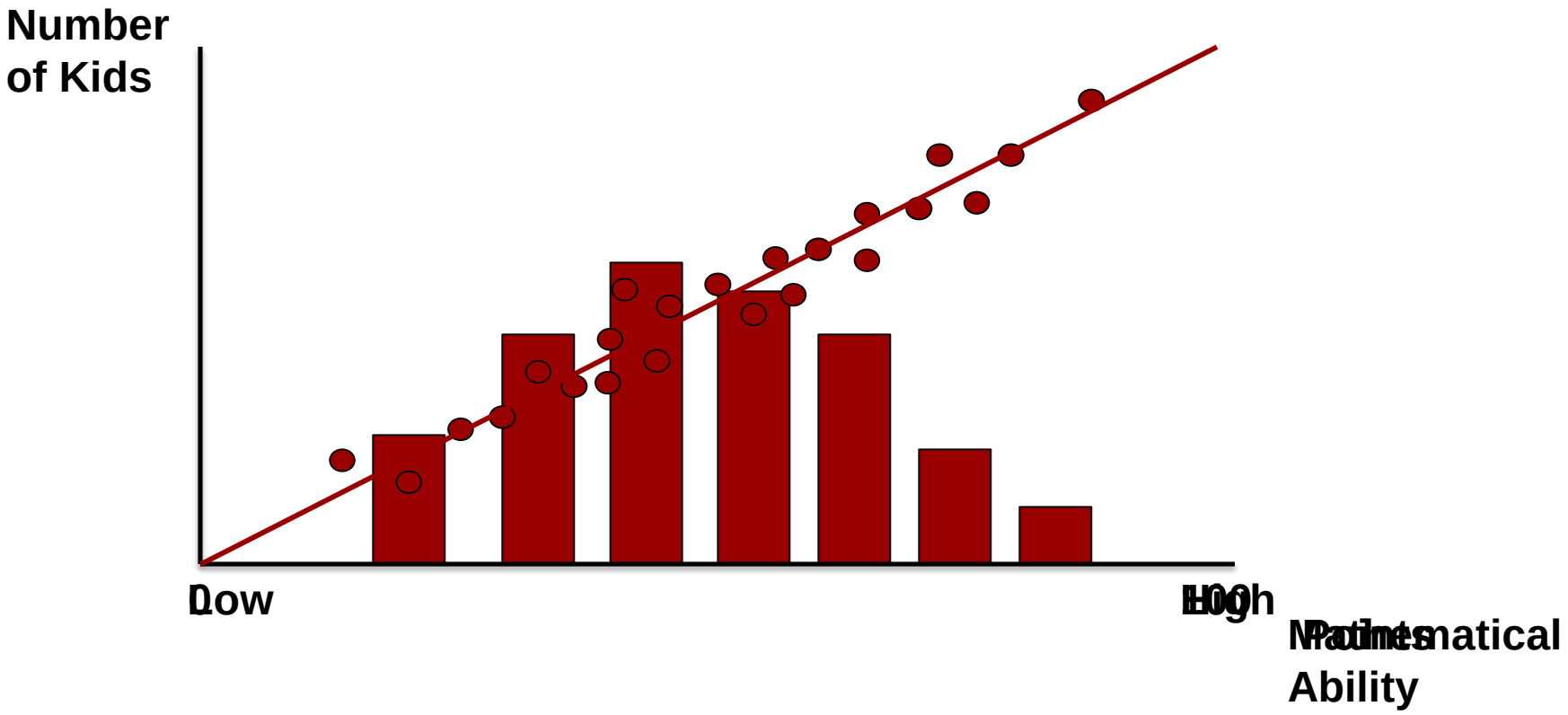
Avoid problems with total score analysis

Provide information and opportunities not available with total score analysis

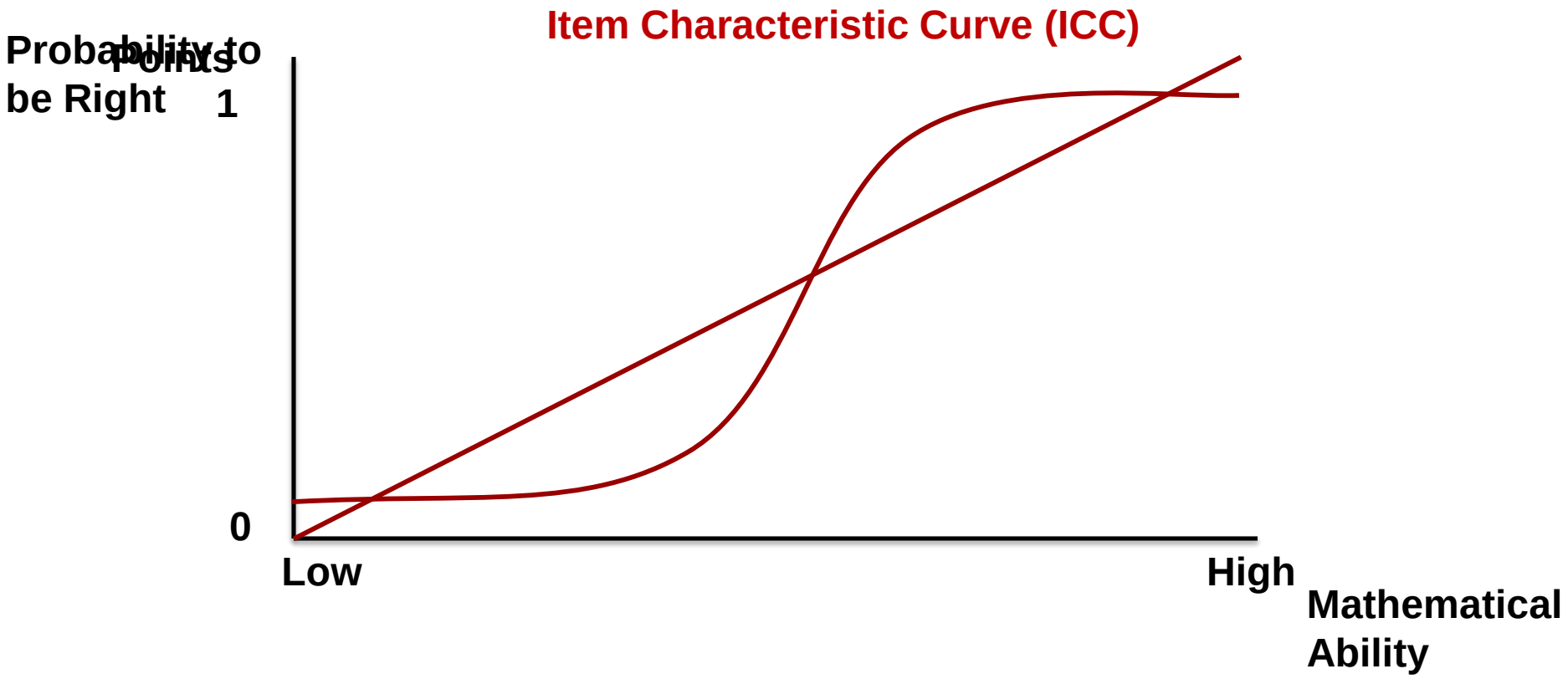
Item Response Theory (IRT) - Concept



Item Response Theory (IRT) - Concept



Item Response Theory (IRT) - Concept



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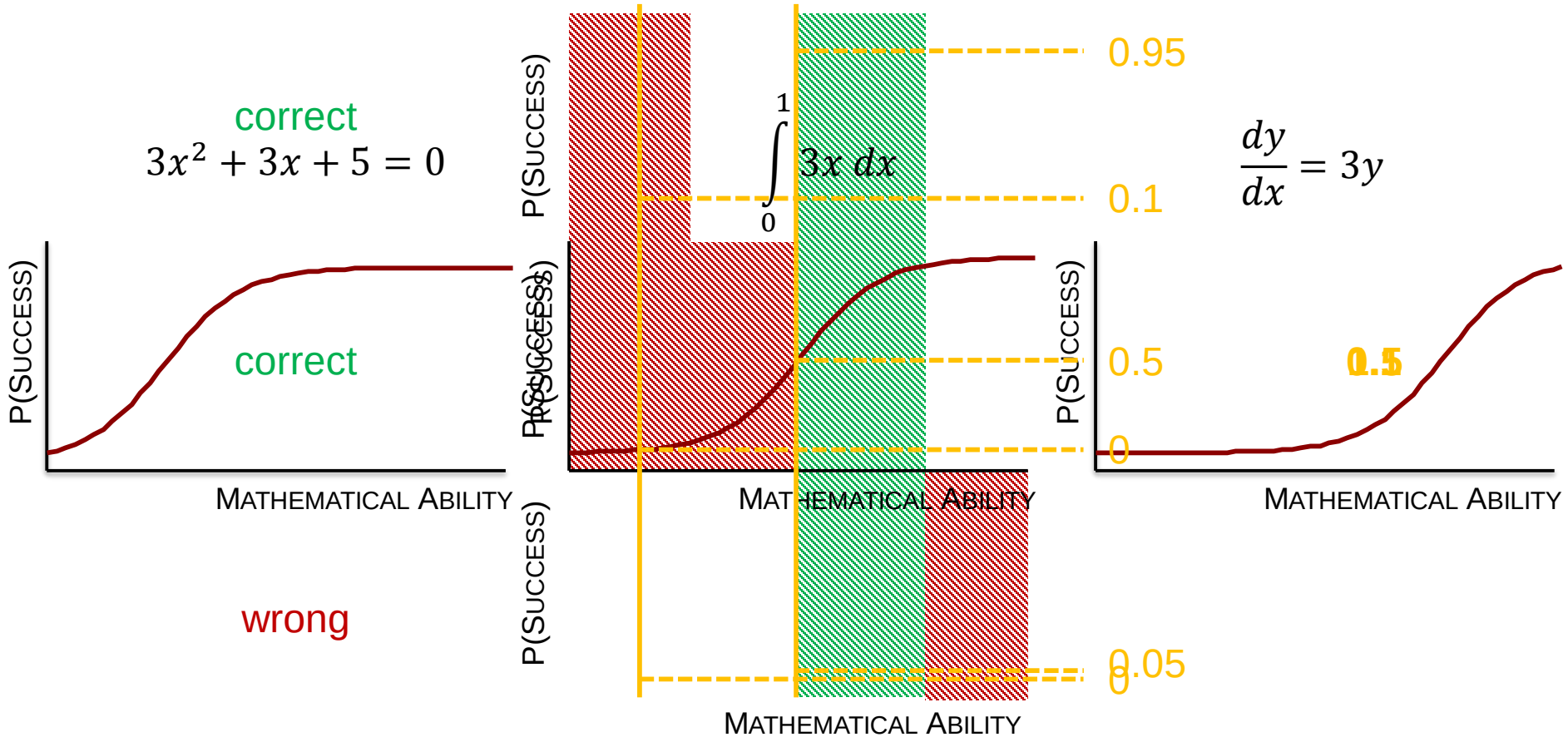
Item Response Theory (IRT) - Concept

- From intuition:
  - Scores are interpreted as measure of ability
  - Mathematical ability can’t be observed and is clearly hypothetical
  - Exam itself is of no particular interest, but acts a surrogate measure for ability

IRT formalizes this intuition

Item Response Theory (IRT) - Concept

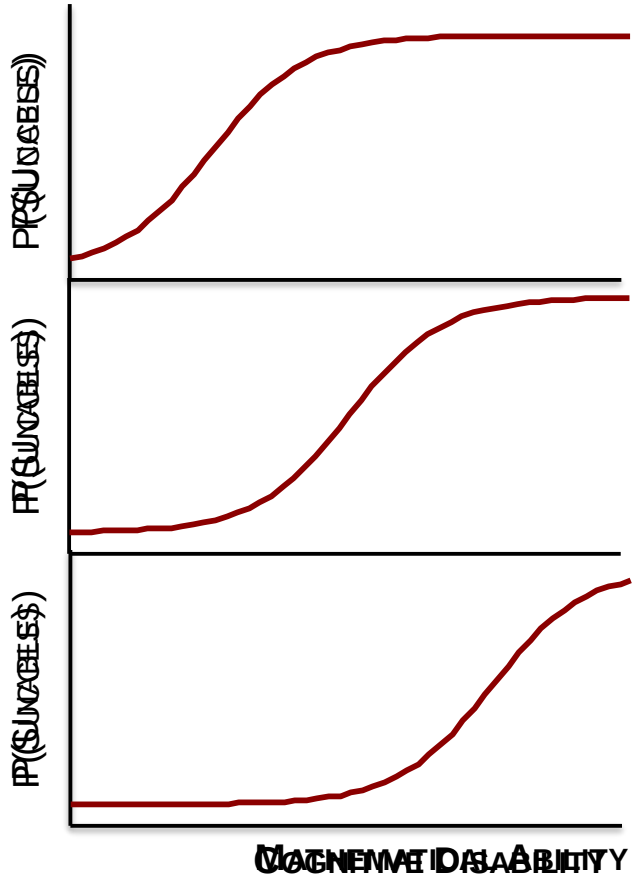


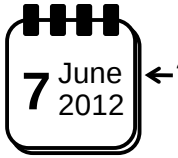
Item Response Theory (IRT) - Concept

$$3x^2 + 3x + 5 = 0$$

$$\int_0^1 3x\,dx$$

$$\frac{dy}{dx} = 3y$$





←? “Name the date”

“Draw a circle”

“Make a fist”

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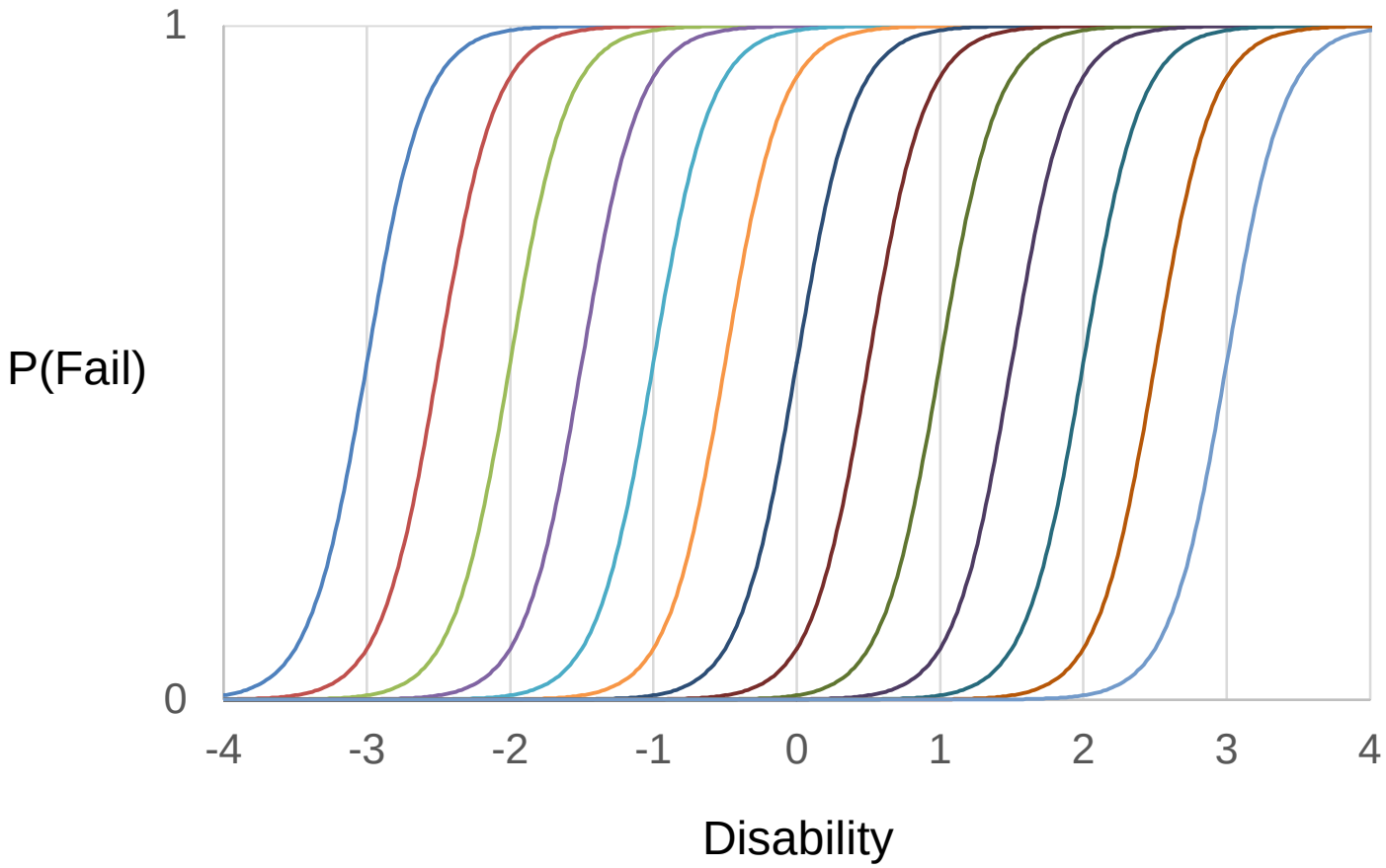
ICCs in a near-perfect composite scale



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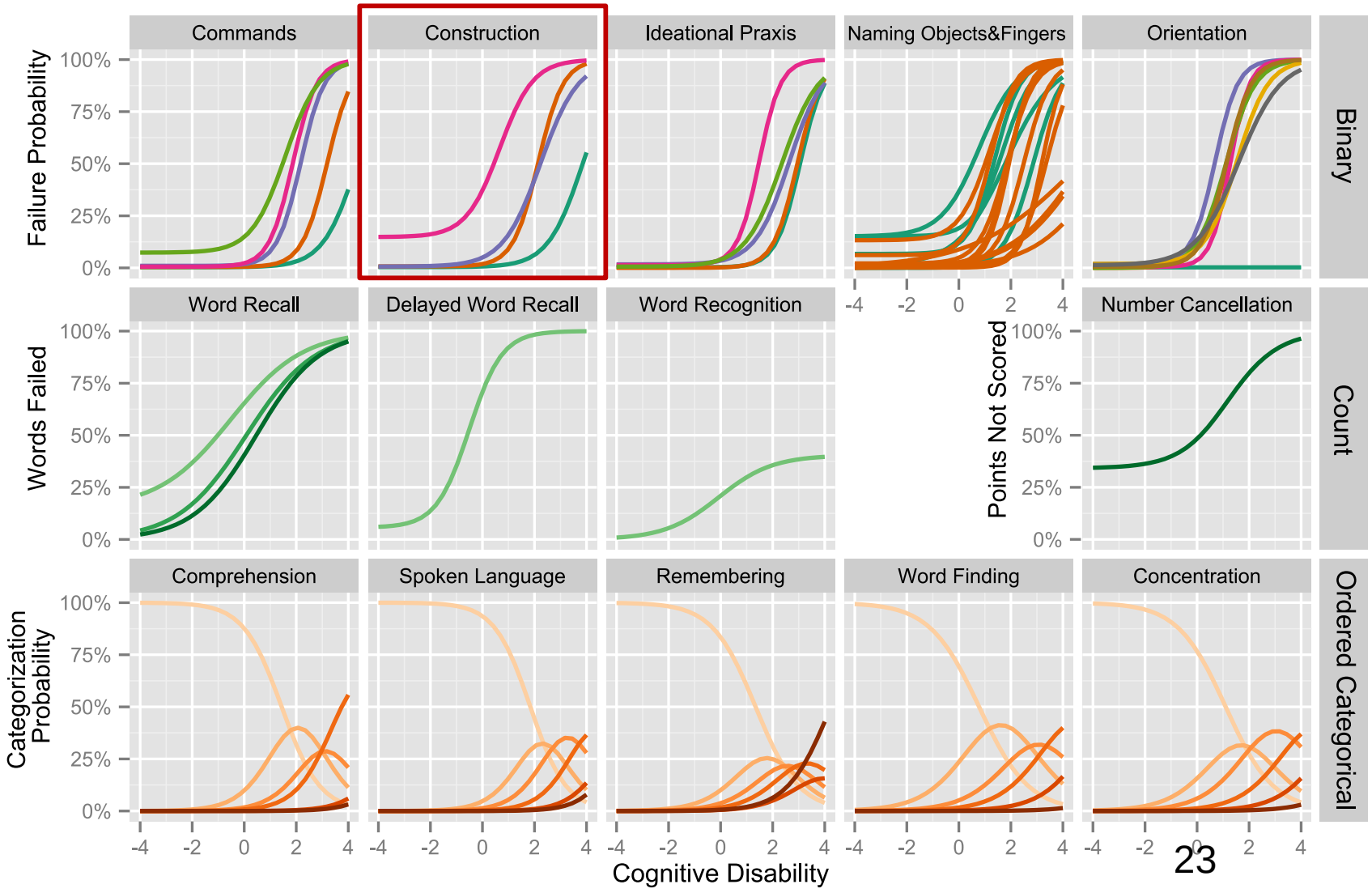
ICCs ADAS-Cog



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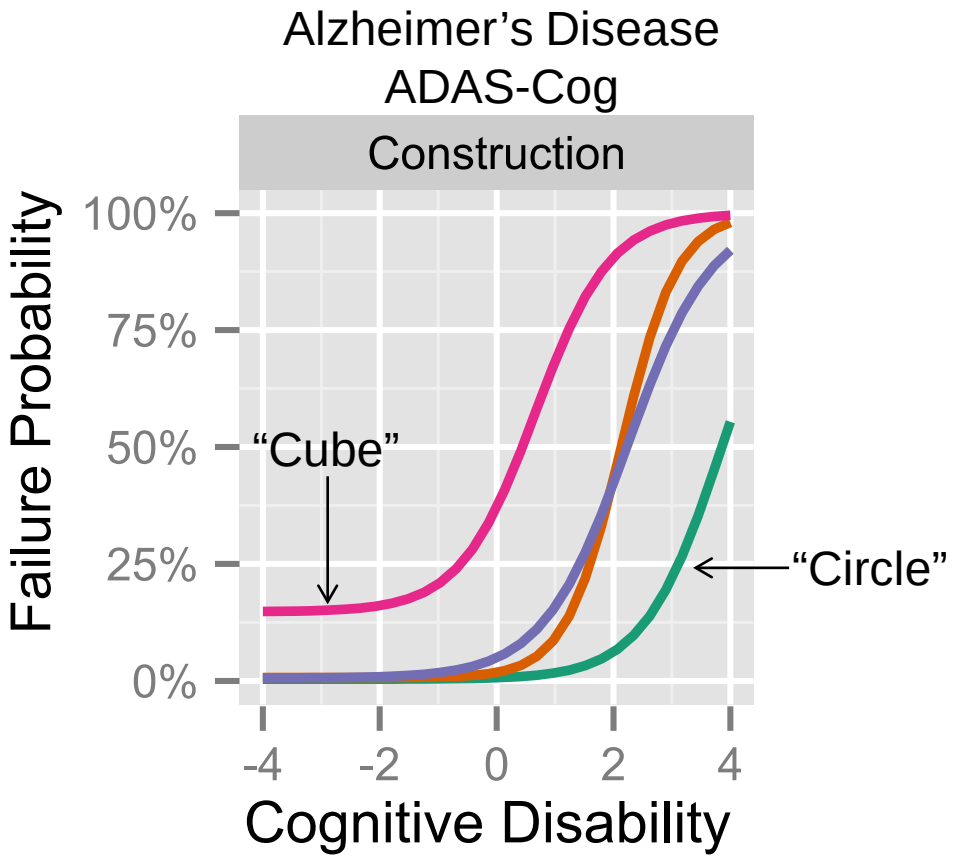
ICCs ADAS-Cog construction



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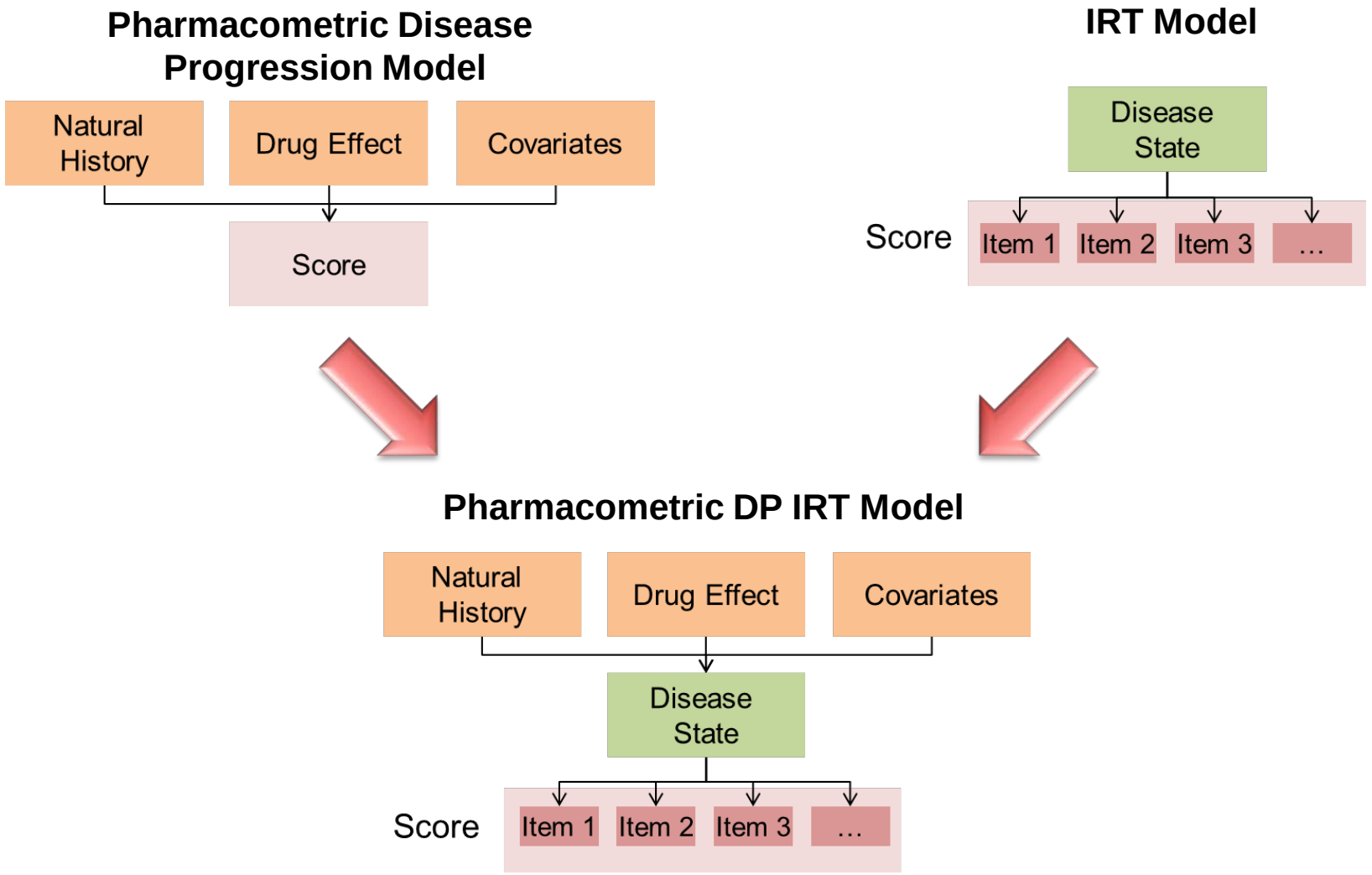
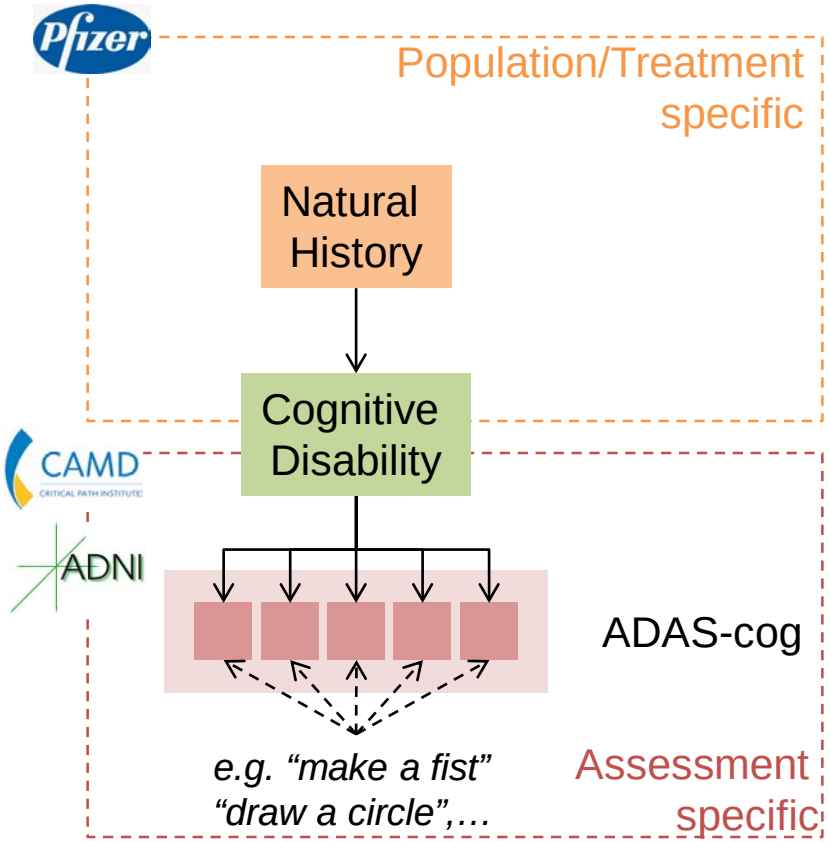
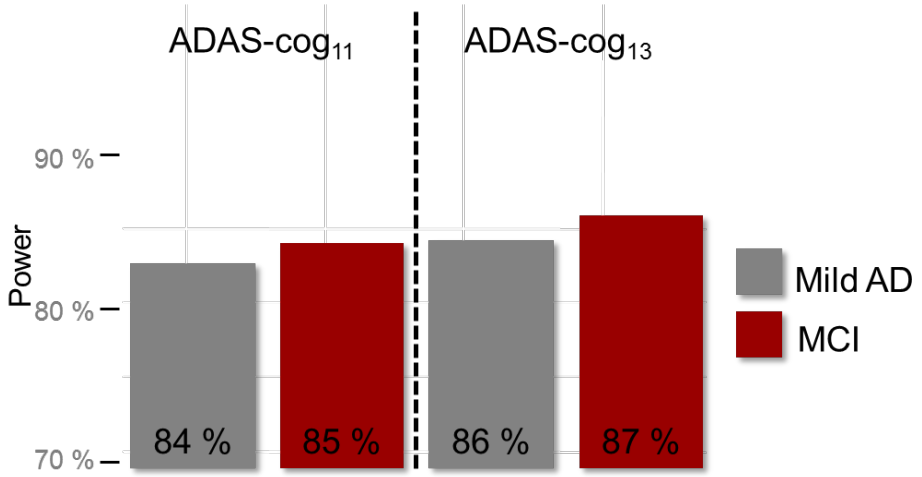
IRT & Pharmacometric Modeling



Example: Alzheimer's Disease



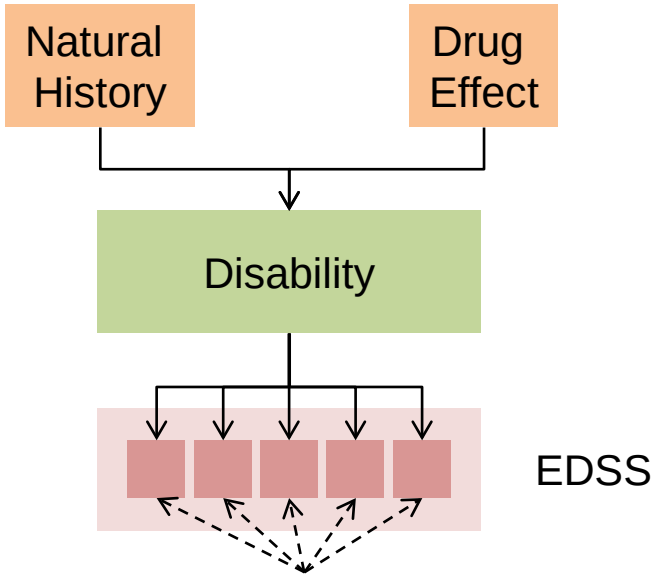
+ Utilize data from public or in-house clinical trial databases
+ Study influence of patient population & assessment variant independent from another



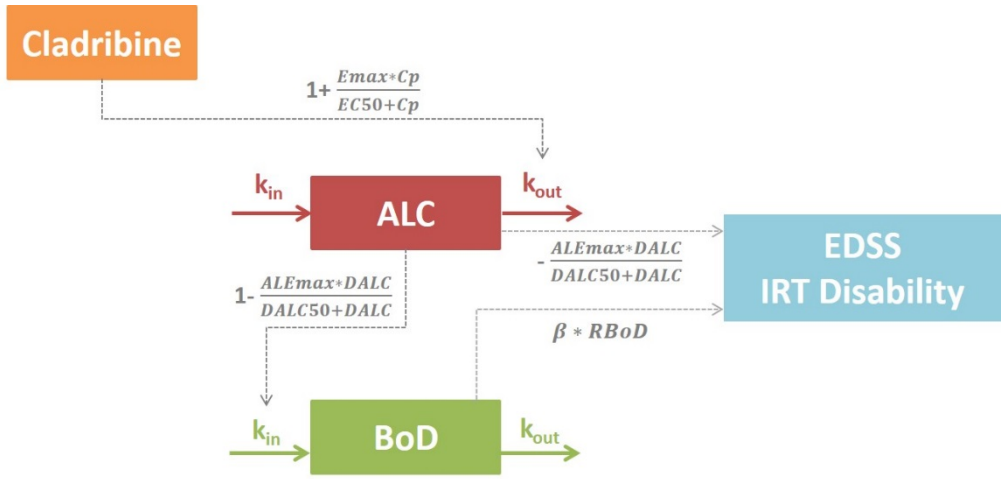
Reference:
Ueckert et al. Pharm Res 31(2013)

Example: Multiple Sclerosis (2)

1st generation model



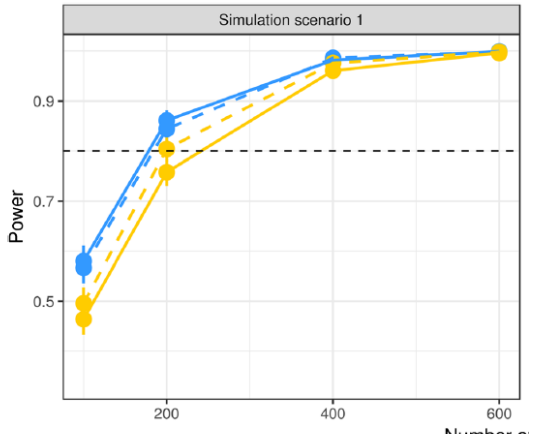
2nd generation model



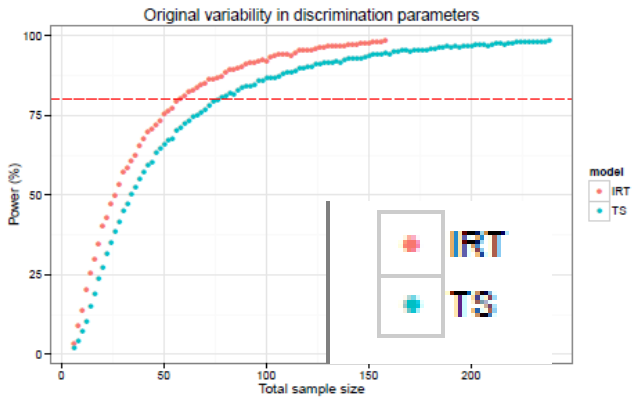
References:
Novakovic et al. AAPSJ (2016)
Novakovic et al PAGE (2017)

Sample size assessment

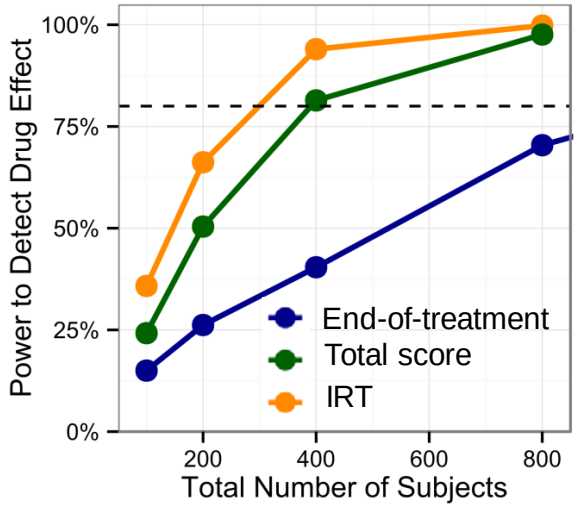
Expected increase in sample size needed for 80% power with total score over IRT



Parkinson's Disease
MDS-UPDRS
+31%



Patient Reported Outcome
FACT-B
+35%



Alzheimer's Disease
ADAS-Cog
+33%

References:
Buatois et al. Pharm Res (2017)
Schindler et al, PAGE (2016)
Ueckert et al. Pharm Res 31 (2013)

Item information

ITEM	Information	% Total Inf.
Cerebellar	2.18	33.98
Pyramidal	1.62	25.28
AmbAid	1.14	17.8
Bowel&Bladder	0.45	7
Brainstem	0.37	5.81
Cerebral	0.29	4.54
Sensory	0.28	4.39
Visual	0.08	1.21

>80%

	Component	Information	% Total
1	Delayed Word Recall	4.79	33.6
2	Word Recall	3.81	26.7
3	Orientation	1.64	11.5
4	Word Recognition	1.40	9.8
5	Naming O&F	0.82	5.7
6	Number Cancellation	0.37	2.6
7	Construction	0.29	2.0
8	Word Finding	0.20	1.4
9	Ideational Praxis	0.18	1.3
10	Concentration	0.18	1.2
11	Remembering	0.16	1.1
12	Comprehension	0.16	1.1
13	Commands	0.15	1.1
14	Spoken Language	0.10	0.7

90 %

<u>Reduced tests options:</u>

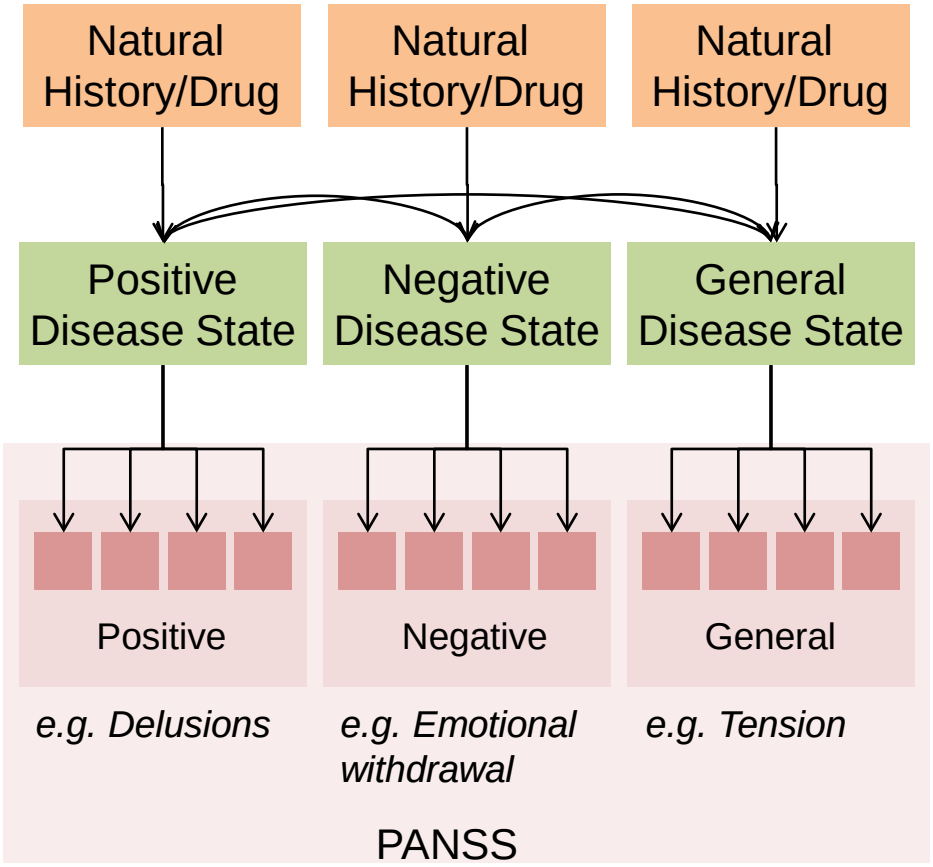
Screening

Trial conduct with limited tests

Trial conduct with individualized dynamic testing

- tests administered to maximize information with few items
- items can be selected to minimize learning effects
- tests can be administered more frequently (device-based)

Example: Schizophrenia



+ Possibility to characterize different disease components in joint model

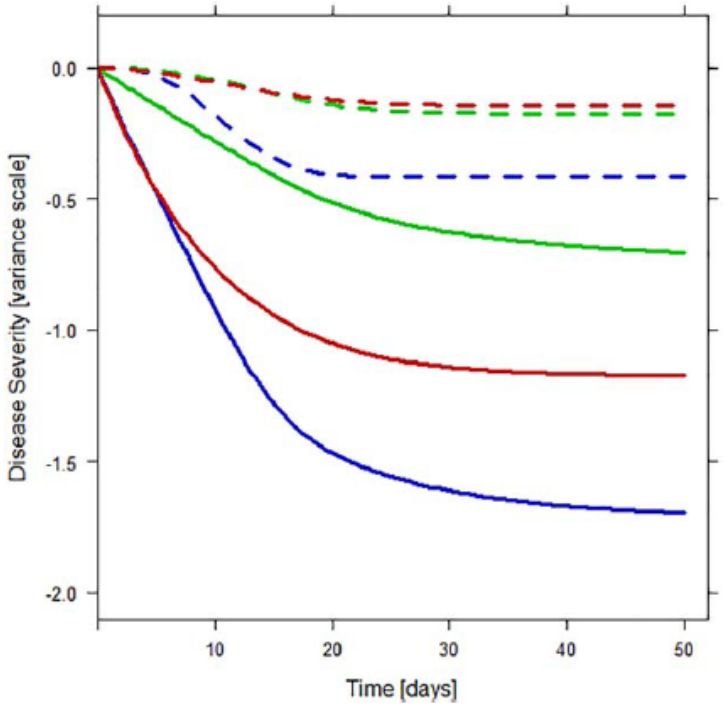
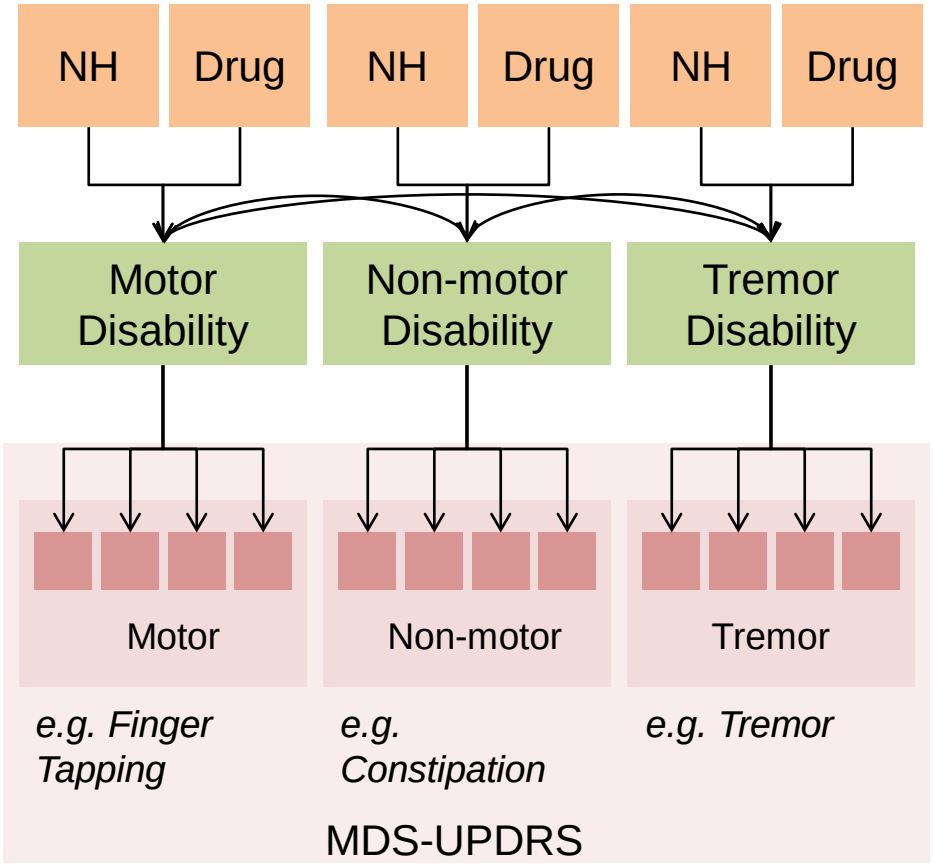


Figure 3 Longitudinal changes in disease state for typical individuals on placebo treatment (dotted lines) and paliperidone treatment (solid lines) for the positive (blue), negative (green), and general (red) subscale, according to our model.

Reference:
Krekels et al. CPT:PSP (2017)

Example: Parkinson's Disease

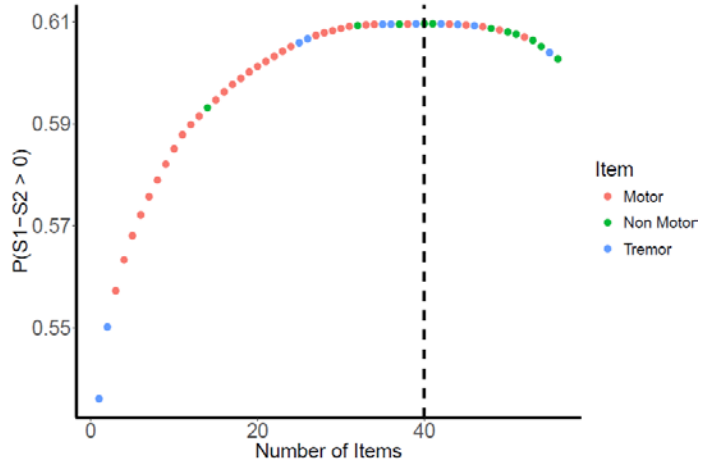


+ Possibility to characterize and identify different drug effects for different components of the assessment

$$D_v(t) = D_v^0 + \alpha_v \cdot t + S_v(t)$$

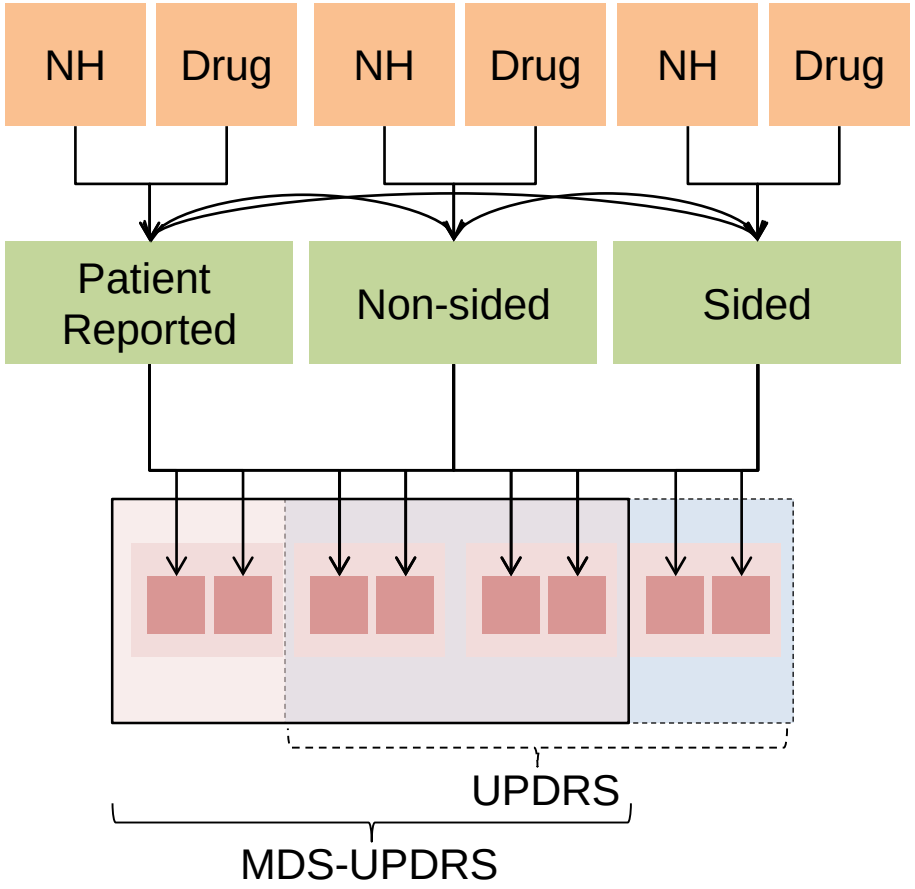
$$S_{Motor}(t) = E_M^0 + \beta_M \cdot (1 - e^{-k_{eq} \cdot t_d})$$
$$S_{Tremor}(t) = E_T^0 + \beta_T \cdot t_d$$
$$S_{N-motor}(t) = E_{NM}^0$$

+ Possibility to maximize power to detect drug effect by choosing subset



References:
Buatois et al. PAGE 24 (2015) Abstr 3417
Buatois et al. PAGE 25 (2016) Abstr 5865

Example: Parkinson's Disease (2)



- Model links established (UPDRS) and novel endpoint (MDS-UPDRS)
  - Leverage historic data
  - Comparison with older compounds
  - Joint framework for complete disease severity range
- Also done in AD for MMSE (often used for screening & diagnosis) & ADAS-cog (regulatory accepted endpoint)
  - Utilize all collected data
  - Leverage clinical routine data
  - Predict clinical endpoint from screening

References:

Gottipati et al. AAPSJ(2017)

Gottipati et al. PAGE 25 (2016) Abstr 5990

Jönsson et al PAGE (2017) Abstr 7236

Parkinson's Disease

- Parkinson Progression Markers Initiative (PPMI) Database:

Unified Parkinson's Disease Rating Scale

PD workbook
THE WEMOVE CLINICIANS' GUIDE TO PARKINSON'S DISEASE

I. Mentation, Behavior and Mood

1. Intellectual Impairment
0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. Activities of Daily Living
(for both "on" and "off")

5. Speech
0 = Normal.

De Novo Parkinson's Disease Subjects	Subjects With Scans Without Evidence of Dopaminergic Deficit (SWEDD)
(n = 423)	*(n = 64)*
Diagnosed ≤ 2 years	*Consented as Parkinson's patients*
***Not** taking any medications for Parkinson's disease*	

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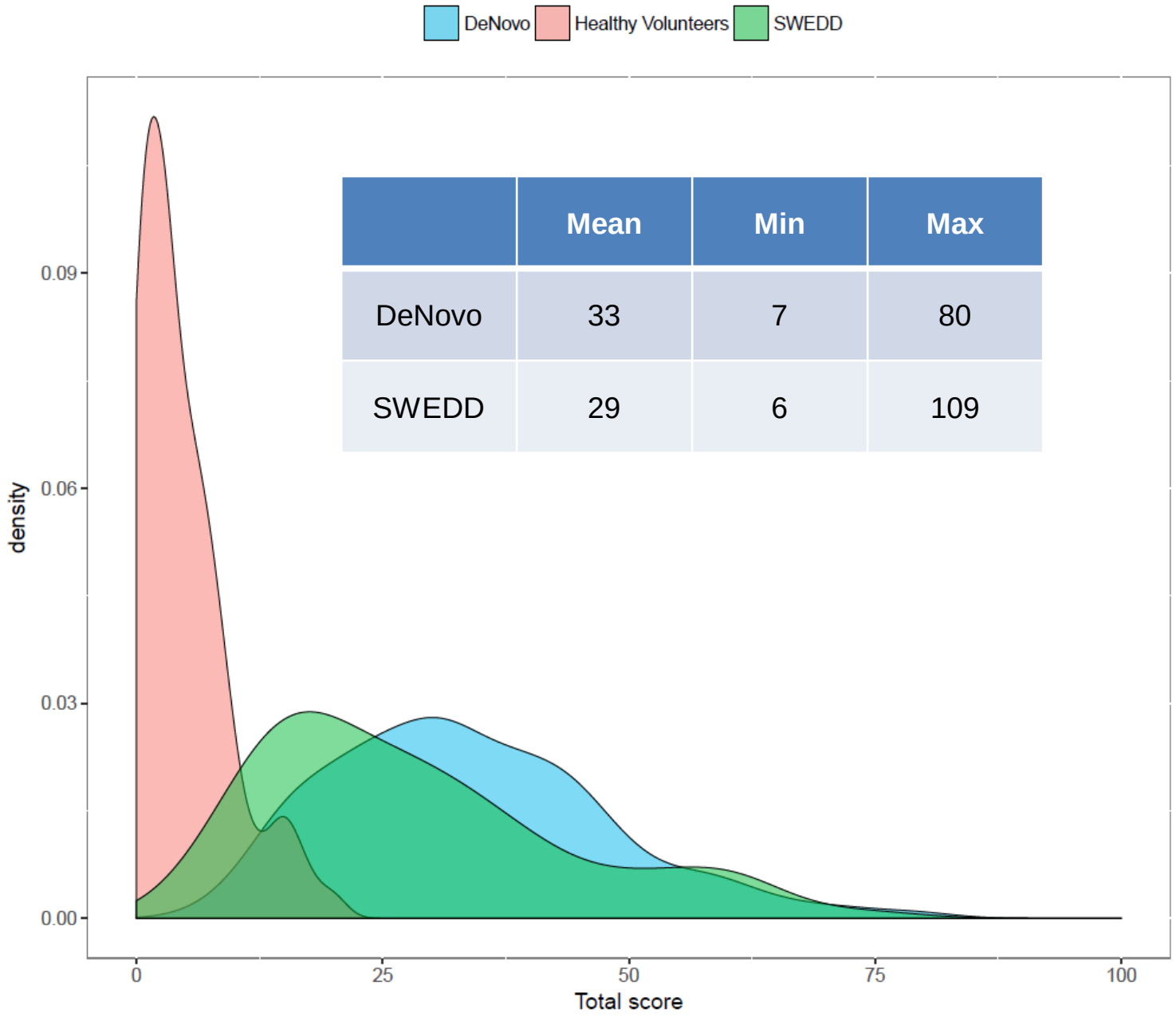

	Mean	Min	Max
DeNovo	33	7	80
SWEDD	29	6	109

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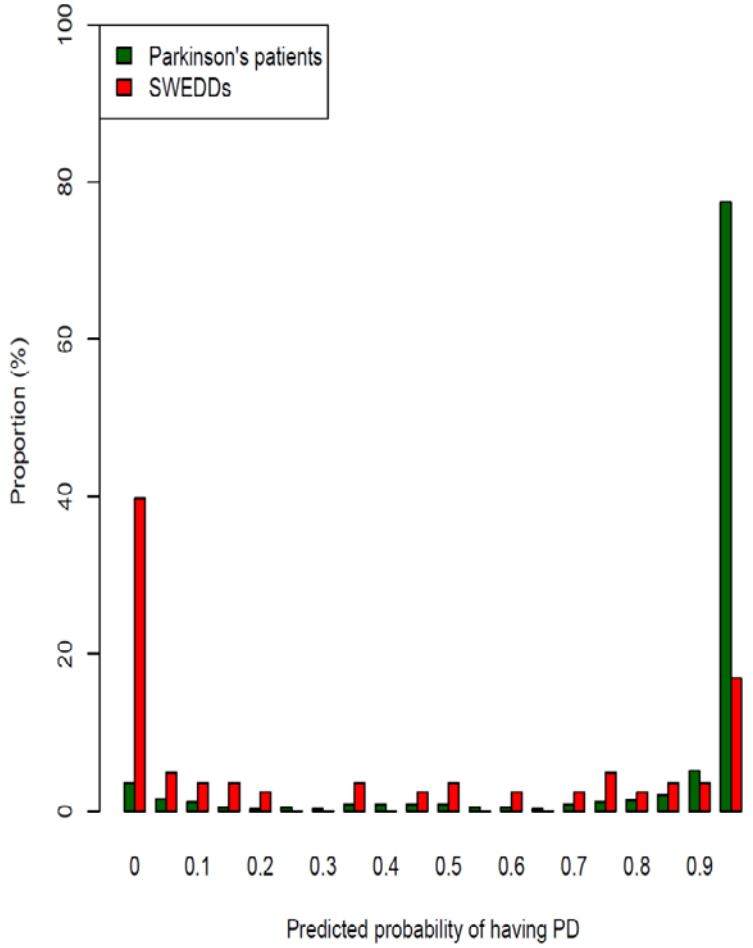
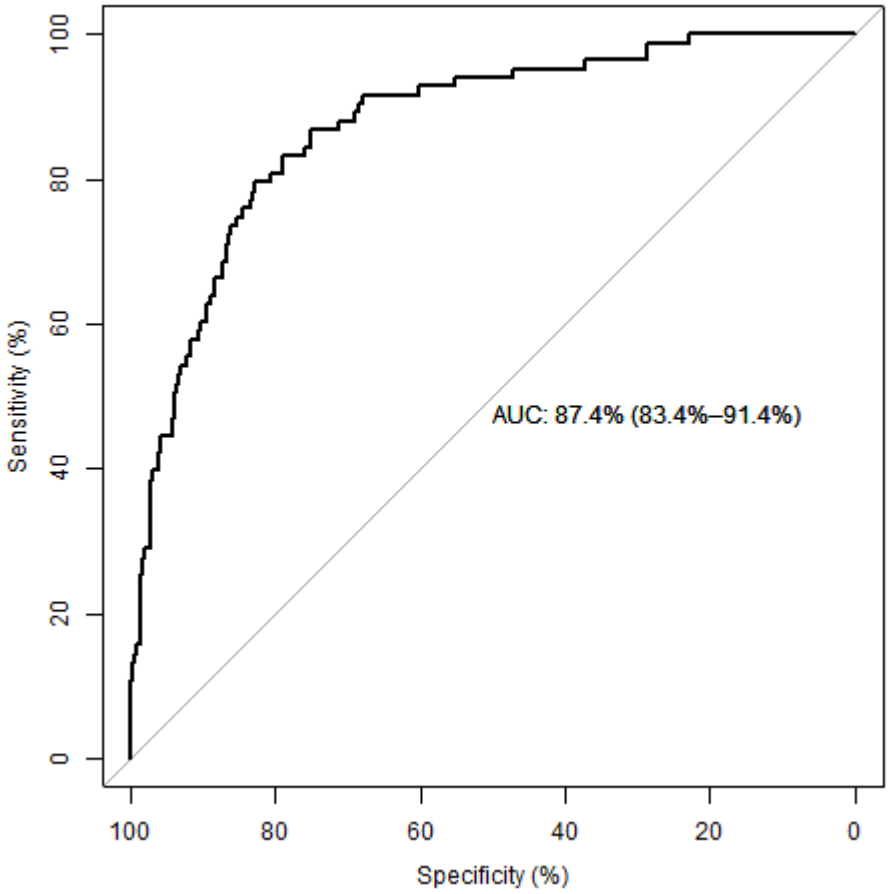
IRM-based diagnosis





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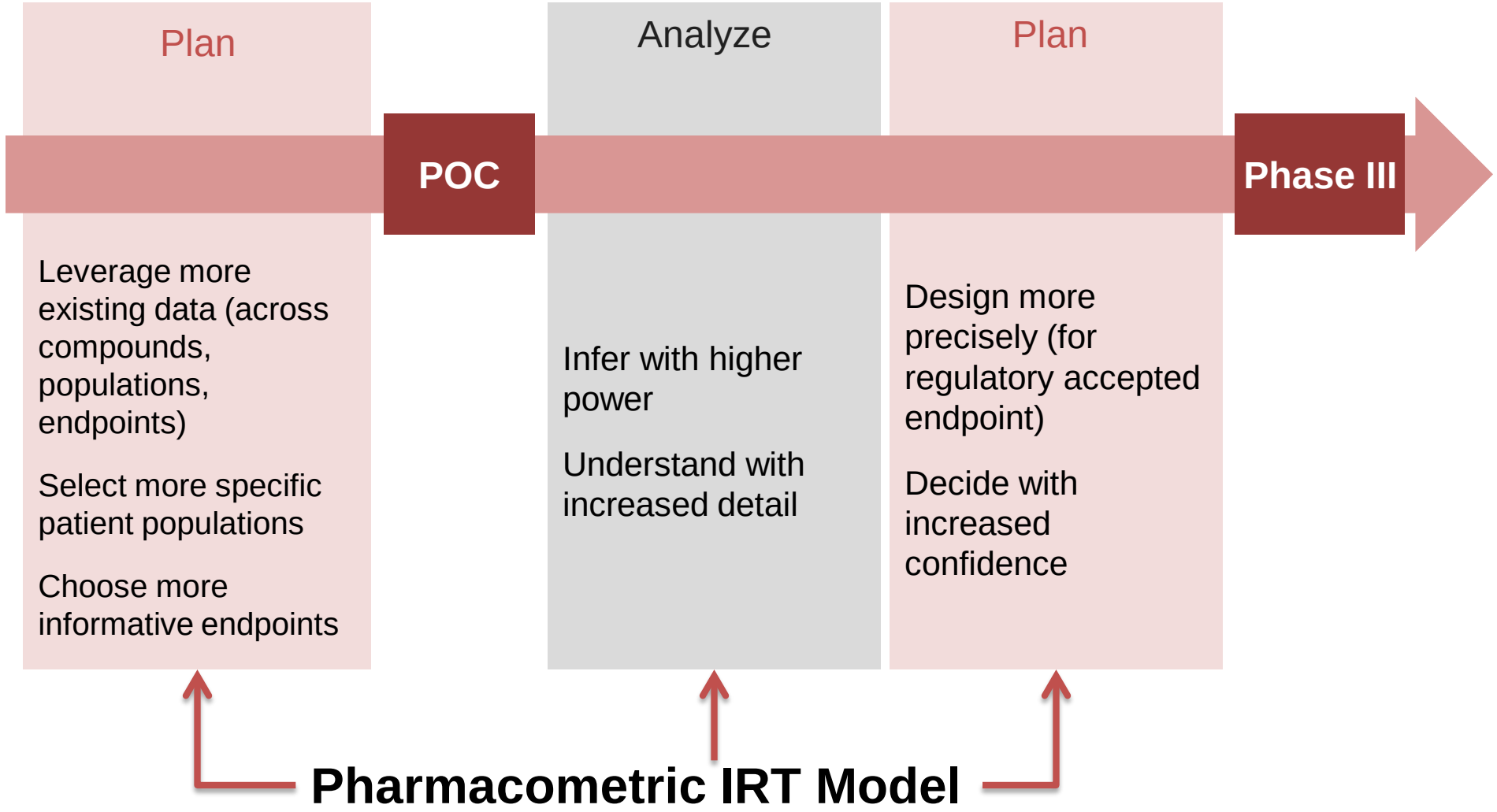
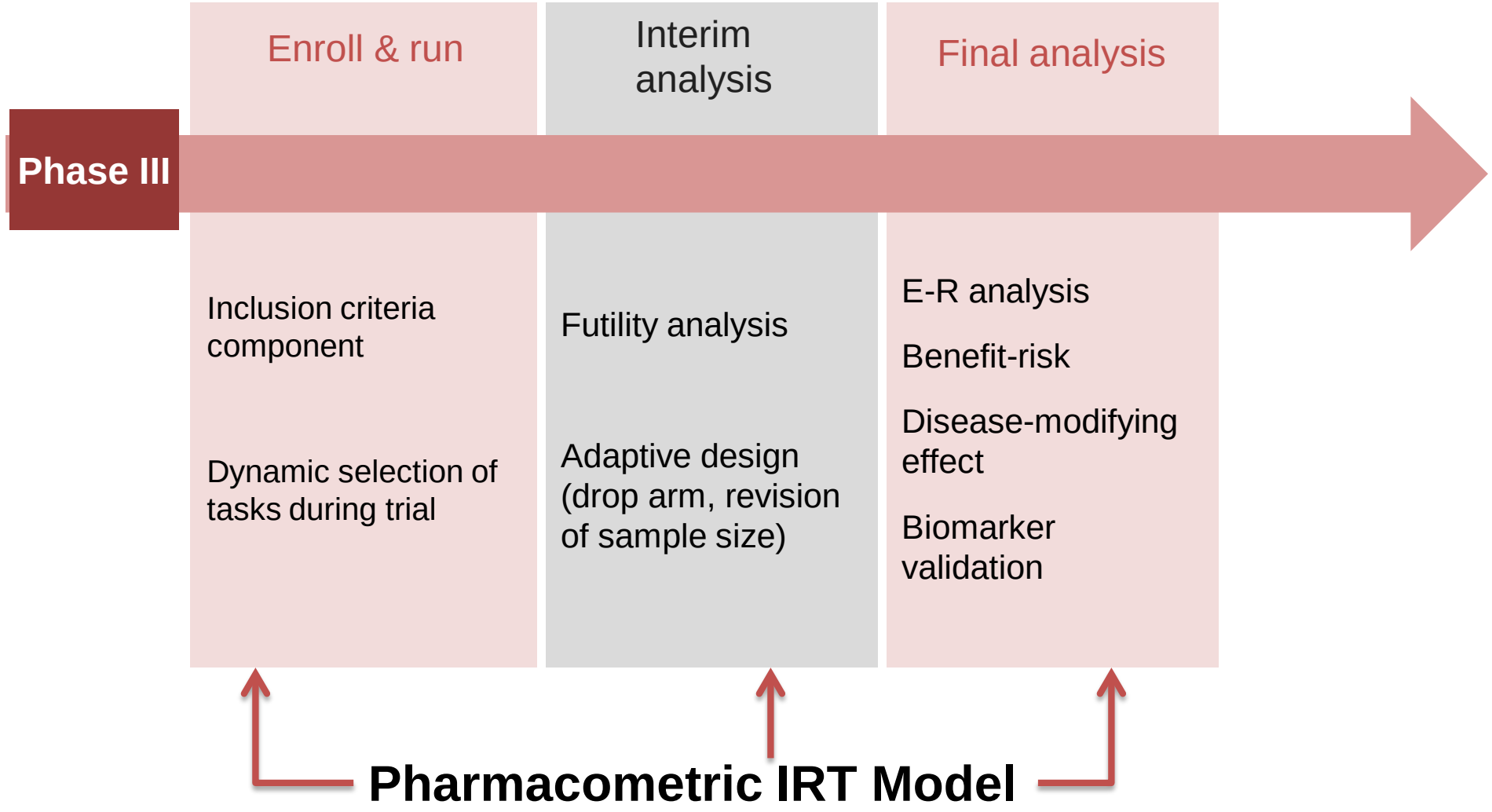
IRT – challenges

- IRT analysis complex
  - Increasing community experience
- IRT model data demanding
  - #Items and #Observations can't be too low
  - Literature models can be used for ICC
- IRT model assumption dependent
  - Assumptions can be assessed through diagnostics
- Software limitations for IRT analysis
  - NONMEM/STAN flexible but offer few built-in facilitations
  - SAS/R has useful functions but restrictive in model scope

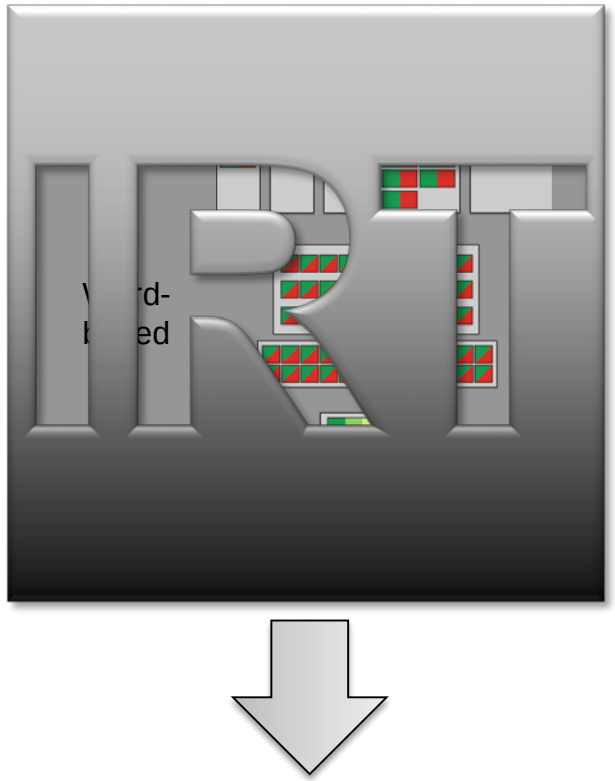
Outlook


Plan
Analyze
Plan
POC
Phase III
Leverage more existing data (across compounds, populations, endpoints)
Select more specific patient populations
Choose more informative endpoints
Infer with higher power
Understand with increased detail
Design more precisely (for regulatory accepted endpoint)
Decide with increased confidence
Pharmacometric IRT Model

Outlook


Enroll & run
Interim analysis
Final analysis
Phase III
Inclusion criteria component
Dynamic selection of tasks during trial
Futility analysis
Adaptive design (drop arm, revision of sample size)
E-R analysis
Benefit-risk
Disease-modifying effect
Biomarker validation
Pharmacometric IRT Model

Conclusions



- Composite assessment data is complex
- Simplification results in loss of information
- IRT allows to capture data complexity
- Combination with pharmacometric modeling yields
  - Higher sensitivity and flexibility to detect drug effect
  - Integrated framework to link different endpoints and populations
  - More precise and versatile trial design
  - …