Key aspects of trials in neurorehabilitation

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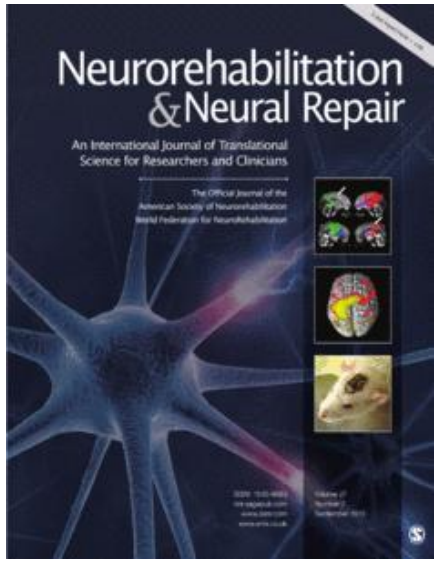
Some issues to be addressed in Neurorehabilitation

- *What are the key aspects of doing evidence-based research in neurorehabilitation?*

- *What are the main concerns (of trials) in neurorehabilitation?*



- Editor: Professor Bruce Dobkin
- Impact Factor: 4.278
- Ranking: 2/63 in Rehabilitation
- 30/191 in Clinical Neurology
- 5-Year Impact Factor: 4.877

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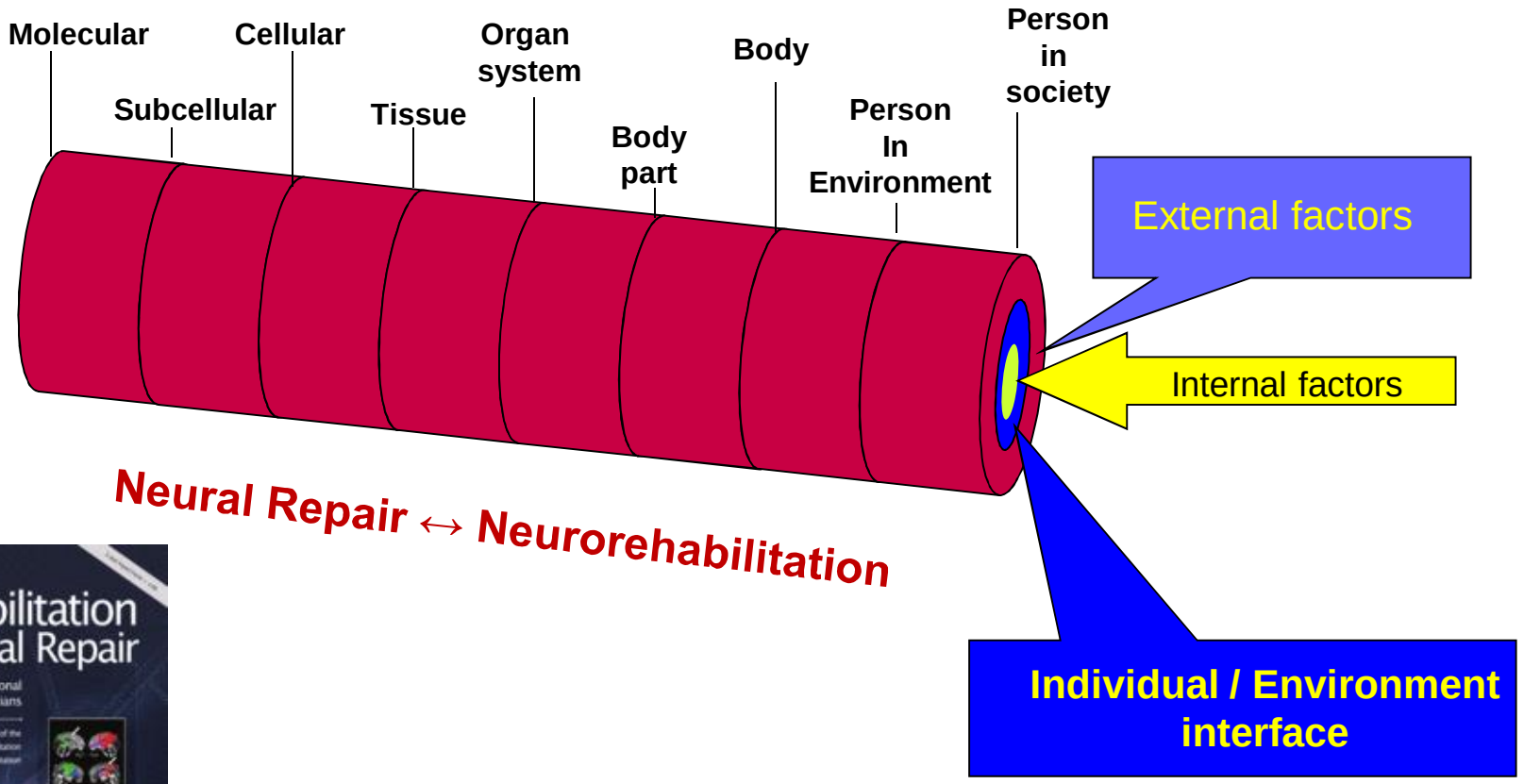
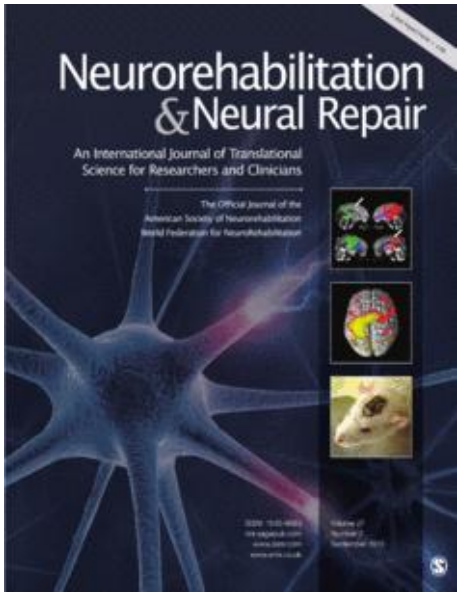
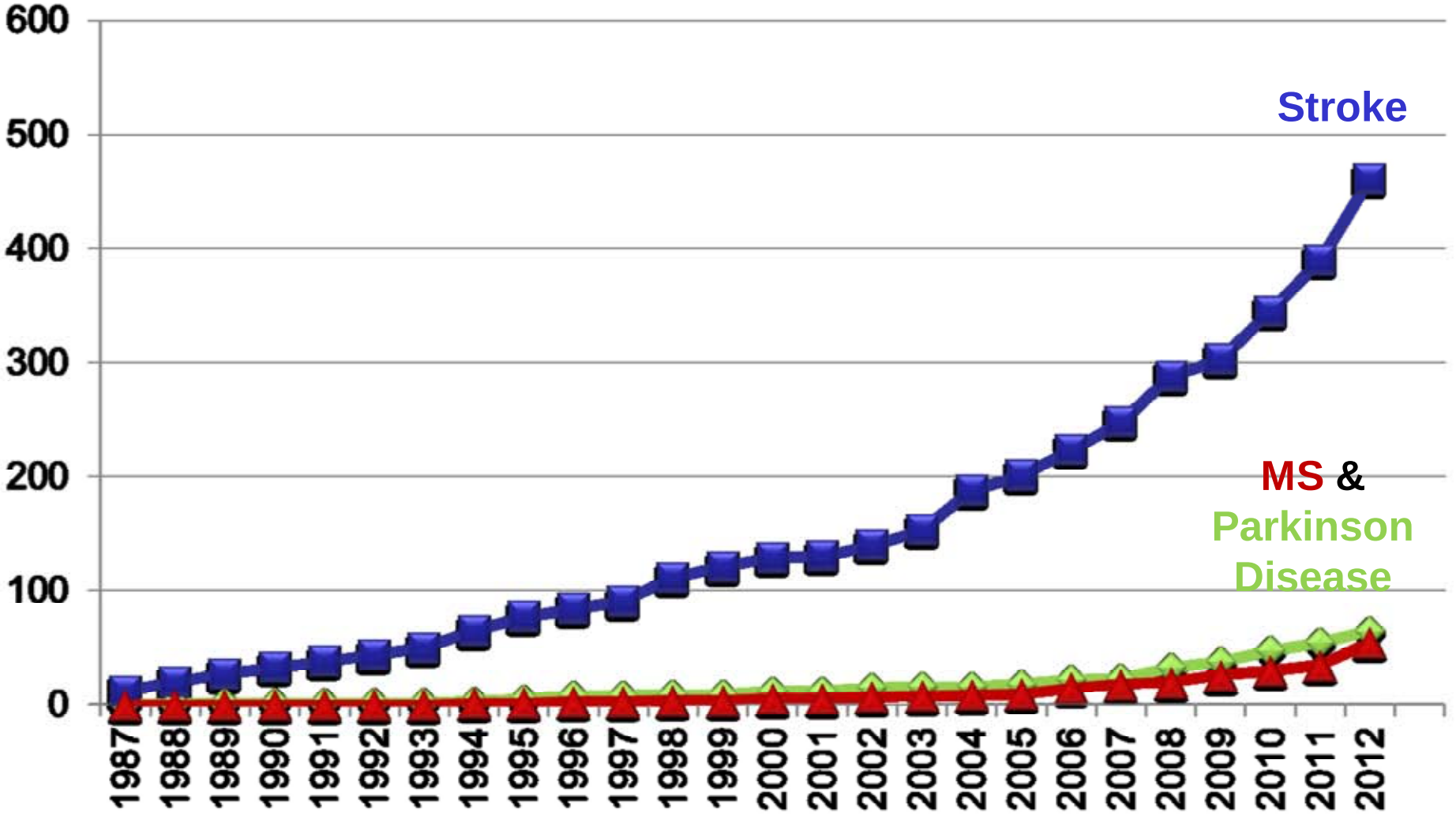
FOCUS of NNR: Translational research





- Randomized Controlled Trials
- Systematic reviews and Meta-analyses
- Prognostic (cohort) studies
- Point of Views

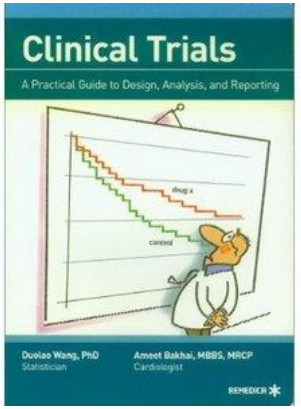
Identified RCTs in the domain of Motor Rehabilitation with respect to MS, PD and Stroke (June 2011)

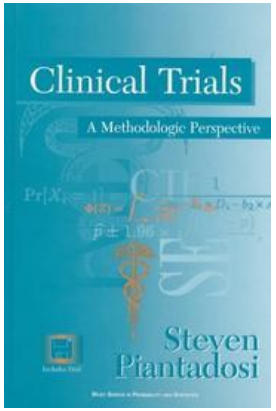


Randomized Controlled Trials

- **CONSORT** (**CON**solidated **S**tandards **O**f **R**eporting **T**rials) statement is an evidence-based, minimum set of recommendations for reporting RCTs.

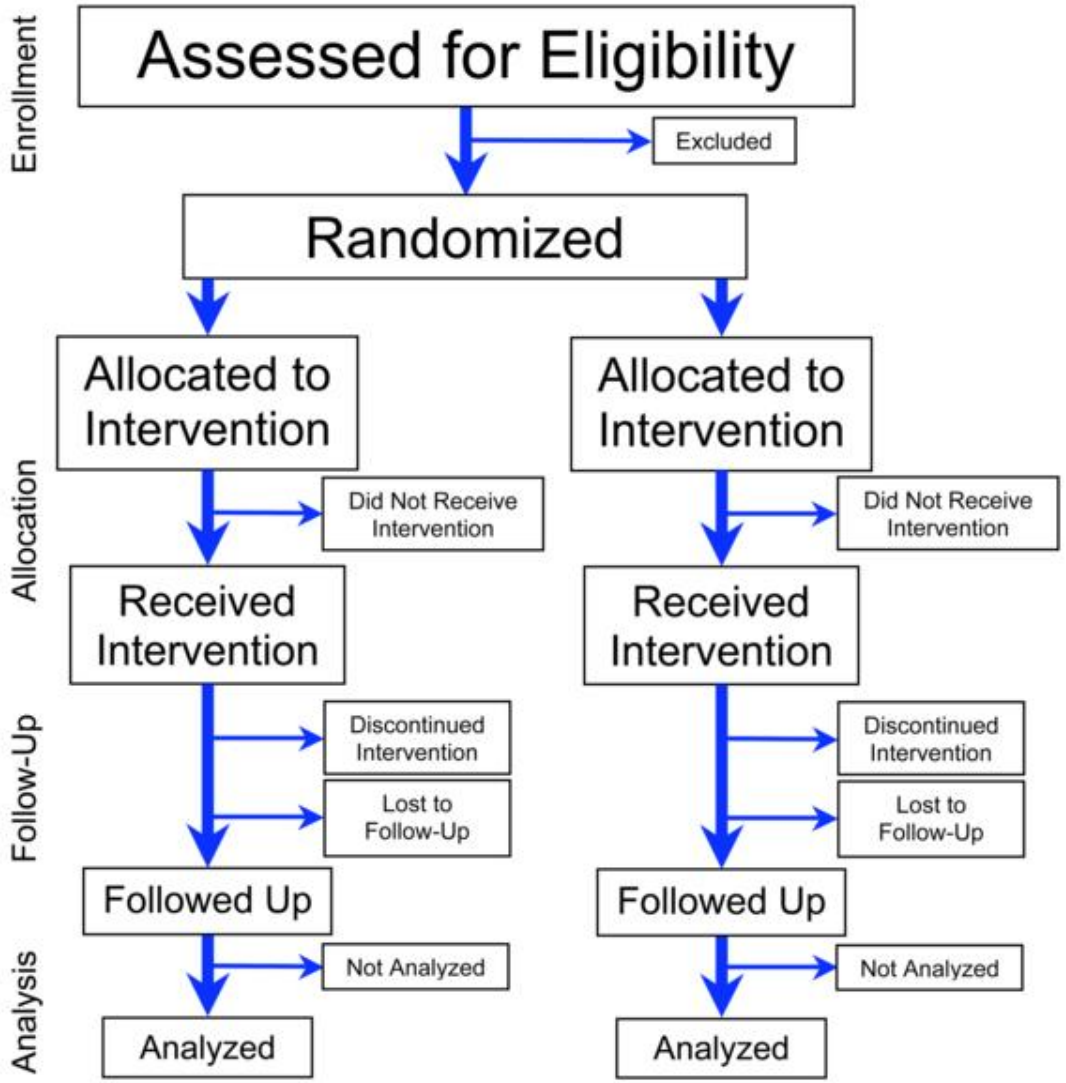
- It offers a standard way (checklist of 22 items) for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation.





http://www.consort-statement.org/

CONSORT STATEMENT 2010



PAPER SECTION And topic	Item	Description	Reported on Page #
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned").	
INTRODUCTION Background	2	Scientific background and explanation of rationale.	
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
Objectives	5	Specific objectives and hypotheses.	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	
Randomization -- Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)	
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	
Recruitment	14	Dates defining the periods of recruitment and follow-up.	
Baseline data	15	Baseline demographic and clinical characteristics of each group.	
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval).	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	
Generalizability	21	Generalizability (external validity) of the trial findings.	
Overall evidence	22	General interpretation of the results in the context of current evidence.	

Systematic reviews and meta-analyses

- The aim of the PRISMA (**P**referred **R**eporting **I**tems for **S**ystematic **R**eviews and **M**eta-**A**nalyses) statement is to help authors report a wide array of systematic reviews to assess the benefits and harms of a health care intervention.

- PRISMA focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses by a checklist of 27 items.

http://www.prisma-statement.org/statement.htm

PRISMA 2009 Checklist

http://www.prisma-statement.org/

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

*P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement.

STROBE Statement

- STROBE is an international collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors involved in the conduct and dissemination of observational studies, with the common aim of **STrengthening the Reporting of OBservational studies in Epidemiology**.

http://www.strobe-statement.org/

27-item checklist according to the STROBE statement:

Study participation D1, Source population and recruitment D2, Inclusion and exclusion criteria D3, Important baseline key characteristics of study sample D4, Prospective design D5, Inception cohort D6, Information about treatment	**Study attrition** A1, Number of loss to follow-up A2, Reasons for loss to follow-up A3, Methods dealing with missing data A4, Comparison completers and non-completers	**Predictor measurement** P1, Definition of predictors P2, Measurement of predictors reliable and valid P3, Coding scheme and cut-off points P4, Data presentation
Outcome measurement O1, Outcome(s) defined O2, Measurement of outcome(s) reliable and valid O3, Coding scheme and cut-off points described O4, Appropriate end-points of observation O5, Data presentation	**Statistical analysis** S1, Strategy for model building described S2, Sufficient sample size S3, Presentation univariable analysis S4, Presentation multivariable analysis S5, Continuous predictors	**Clinical performance/validity** C1, Clinical performance C2, Internal validation C3, External validation

Veerbeek JM et al, Early prediction of ADLs outcome after stroke: A systematic review. Stroke. 2011 May;42(5):1482-8.

1, Positive; 0, Negative; ?, Partial/unknown

Topical Review

Section Editors: Michael Brainin, MD, PhD, and Richard D. Zorowitz, MD

Early Prediction of Outcome of Activities of Daily Living After Stroke

A Systematic Review

Janne M. Veerbeek, MSc; Gert Kwakkel, PhD; Erwin E.H. van Wegen, PhD; Johannes C.F. Ket; Martijn W. Heymans, PhD

Background and Purpose—Knowledge about robust and unbiased factors that predict outcome of activities of daily living (ADL) is paramount in stroke management. This review investigates the methodological quality of prognostic studies in the early poststroke phase for final ADL to identify variables that are predictive or not predictive for outcome of ADL after stroke.

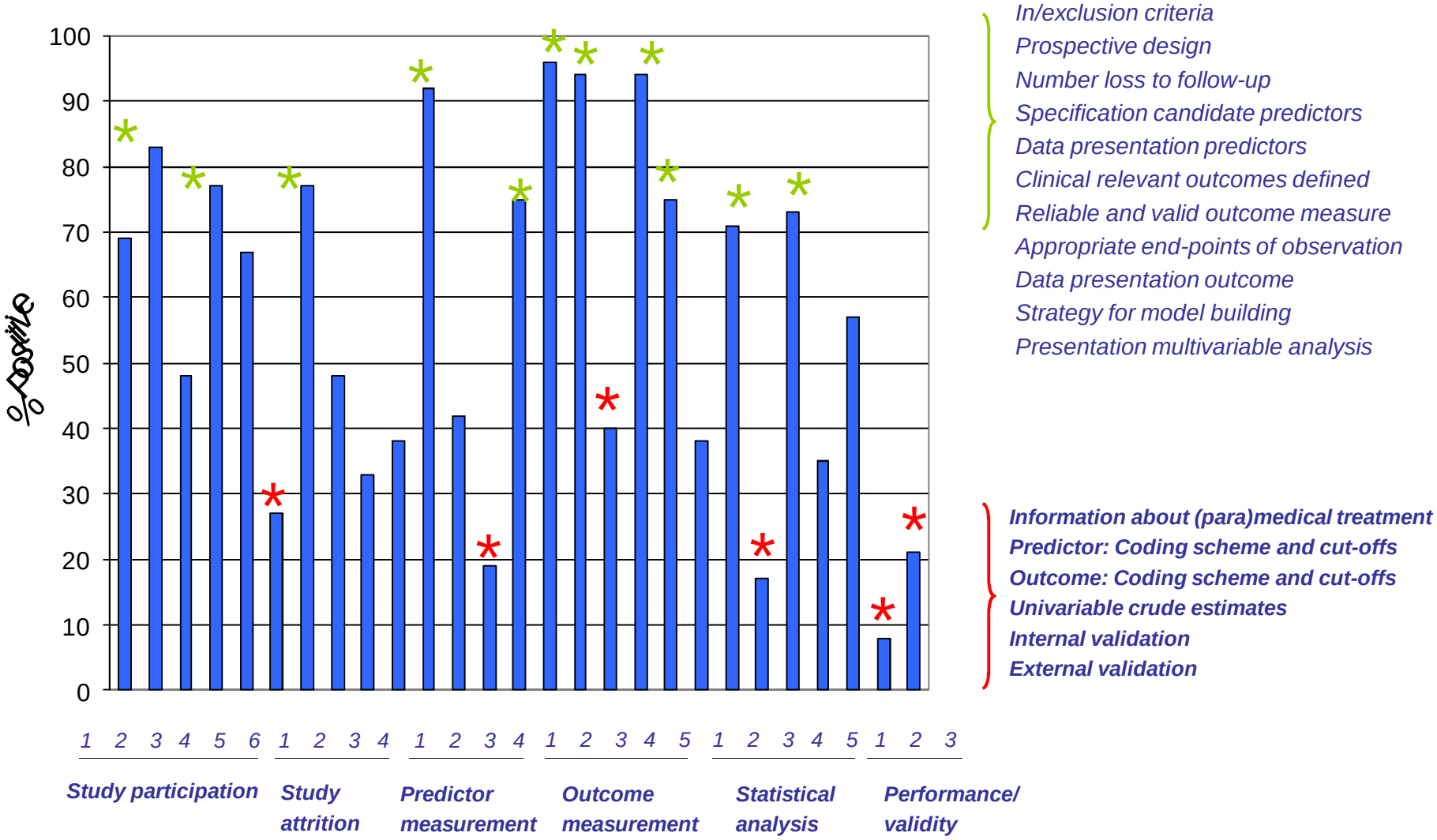
Methods—PubMed, Ebsco/Cinahl and Embase were systematically searched for prognostic studies in which stroke patients were included ≤2 weeks after onset and final outcome of ADL was determined ≥3 months poststroke. Risk of bias scores were used to distinguish high- and low-quality studies and a qualitative synthesis was performed.

Results—Forty-eight of 8425 identified citations were included. The median risk of bias score was 17 out of 27 (range, 6–22) points. Most studies failed to report medical treatment applied, management of missing data, rationale for candidate determinants and outcome cut-offs, results of univariable analysis, and validation and performance of the model, making the predictive value of most determinants indistinct. Six high-quality studies showed strong evidence for baseline neurological status, upper limb paresis, and age as predictors for outcome of ADL. Gender and risk factors such as atrial fibrillation were unrelated to this outcome.

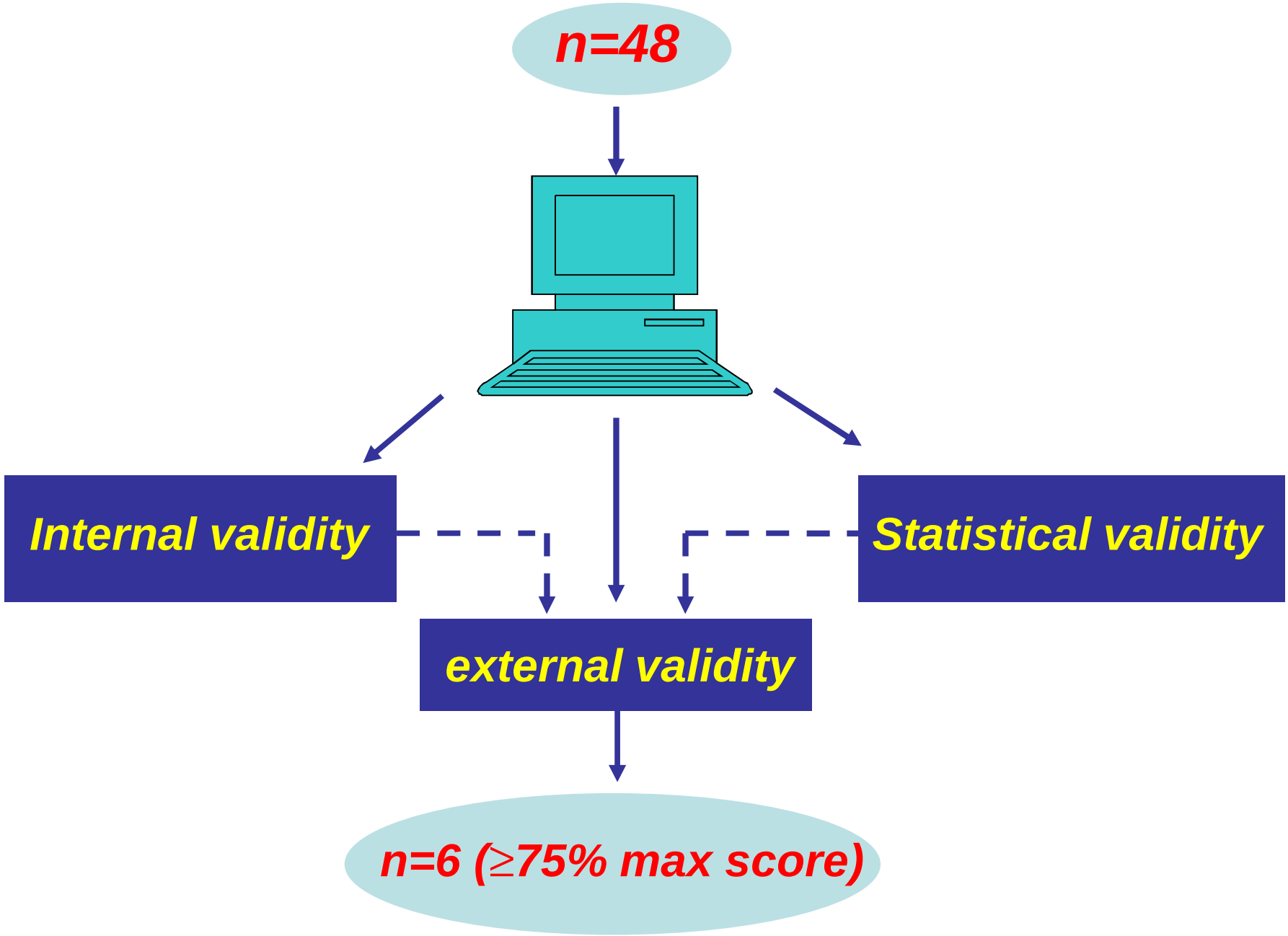
Conclusions—Because of insufficient methodological quality of most prognostic studies, the predictive value of many clinical determinants for outcome of ADL remains unclear. Future cohort studies should focus on early prediction using simple models with good clinical performance to enhance application in stroke management and research. **(*Stroke*. 2011;42:1482-1488.)**

Key Words: activities of daily living ■ prognosis ■ review ■ stroke

Quality assessment of 48 studies predicting outcome of ADL after stroke (following the STROBE guidelines)



Veerbeek JM et al, Stroke. 2011 May;42(5):1482-8.



Veerbeek JM et al, Stroke. 2011 May;42(5):1482-8.

COSMIN standards

COSMIN stands for COnsensus?Qased Standards for the selection of health Measurement INstruments.

Qual Life Res (2012) 21:925–944
DOI 10.1007/s11136-011-0009-2

REVIEW

Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties

Roy G. Elbers · Marc B. Rietberg · Erwin E. H. van Wegen · John Verhoef · Sharon F. Kramer · Caroline B. Terwee · Gert Kwakkel

Accepted: 2 September 2011 / Published online: 20 October 2011

Abstract

Purpose To critically appraise, compare and summarize the measurement properties of self-report fatigue questionnaires validated in patients with multiple sclerosis (MS), Parkinson's disease (PD) or stroke.

Methods MEDLINE, EMBASE, PsycINFO, CINAHL and SPORTdiscus were searched. The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist was used to assess the methodological quality of studies. A qualitative data synthesis was performed to rate the measurement properties for each questionnaire.

Results Thirty-eight studies out of 5,336 records met the inclusion criteria, evaluating 31 questionnaires. Moderate evidence was found for adequate internal consistency and structural validity of the Fatigue Scale for Motor and Cognitive functions (FSMC) and for adequate reliability and structural validity of the Unidimensional Fatigue Impact Scale (U-FIS) in MS.

Conclusions We recommend the FSMC and U-FIS in MS. The Functional Assessment of Chronic Illness Therapy Fatigue subscale (FACIT-F) and Fatigue Severity Scale (FSS) show promise in PD, and the Profile of Mood States Fatigue subscale (POMS-F) for stroke. Future studies should focus on measurement error, responsiveness and interpretability. Studies should also put emphasis on providing input for the theoretical construct of fatigue, allowing the development of questionnaires that reflect generic and disease specific symptoms of fatigue.

Electronic supplementary material The online version of this article (doi:10.1007/s11136-011-0009-2) contains supplementary material, which is available to authorized users.

R. G. Elbers (✉) · J. Verhoef
Department of Physiotherapy, University of Applied Sciences

Some issues to be addressed in Neurorehabilitation

- *What are the key aspects of doing evidence-based research in neurorehabilitation?*

Ø *What are the main concerns (of trials) in neurorehabilitation?*

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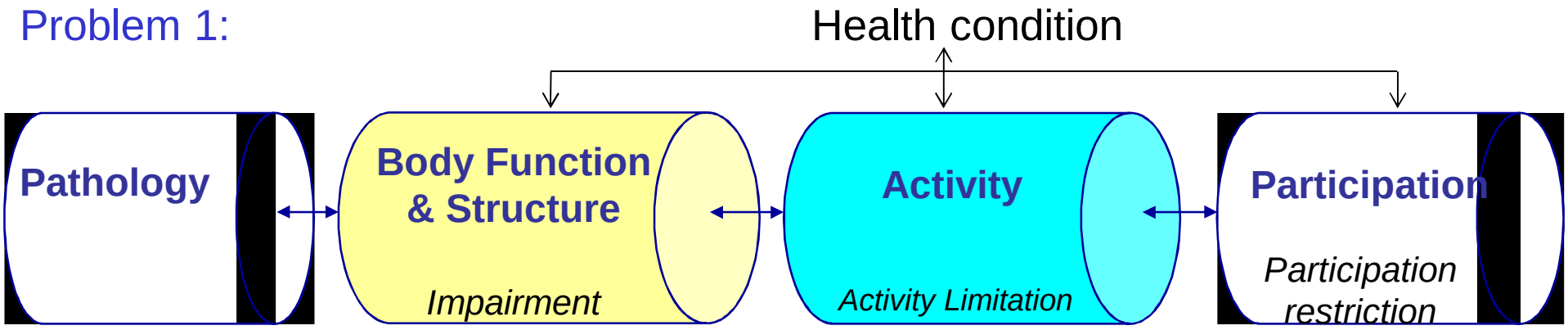
Problem 1:



Stroke

§MRC scale
§Motricity Index
§Brunnstrom Stages
§Fugl-Meyer Assessment Score
§Notthingham Sensory Assessment
§(modified) Ashworth scale
§Chedoke McMaster Motor Assessment Stroke Scale
§Tardieu Scale
§Rivermead Motor Assessment
§Scandinavian Stroke Scale
§NIHSS
§Cincinnati Stroke Scale
§Trunk Impairment Scale
§Hemispheric Stroke Scale

•Functional Reach
•Berg-Balance Scale
•Timed-Balance Test
•Timed-Get-up & Go
•10-meter gait speed
•1, 5, 6, 12 min walking tests
•Trunk Control Test
•Nine Hole Peg Test
•Action Research Arm test
•Frenchay Arm Test
•Box and Block test
•Jebsen handfunction test
•ABIL-hand
•Functional Ambulation Categories (FAC)
•Rivermead Mobility Index (RMI)
•Barthel Index (BI); mBI
•FIM
•modified Rankin Scale
•SIS (vs. 2.0 & 3.0)

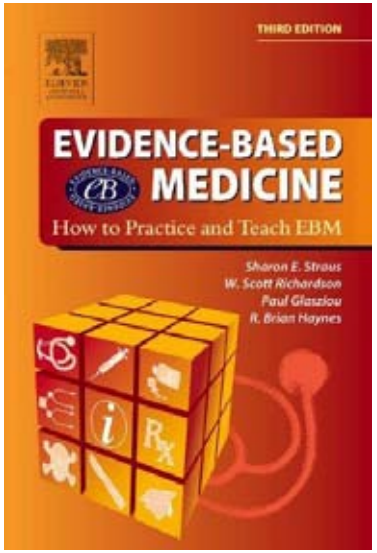
•FSS, MFI,
•CIS-20r
•HADS
•SIP-136, SIP-68, SIP-30
•SF-36
•EuroQoL-5D
•SIS (vs. 2.0 & 3.0)
•SA-SIP-30
•SSQL
•Rankin Scale
•Frenchay Activities Index
•Nottingham Extended ADL (NEADL)
•Notthingham Health Profile

Problem 2:

Number of RCTs in the domain of motor rehabilitation post stroke

Search (June 2011)

- Pubmed 13407 P
- Embase + 4281 P
- CINAHL + 419 P
- Cochrane +1676 P
- Sportdisc + 194 P



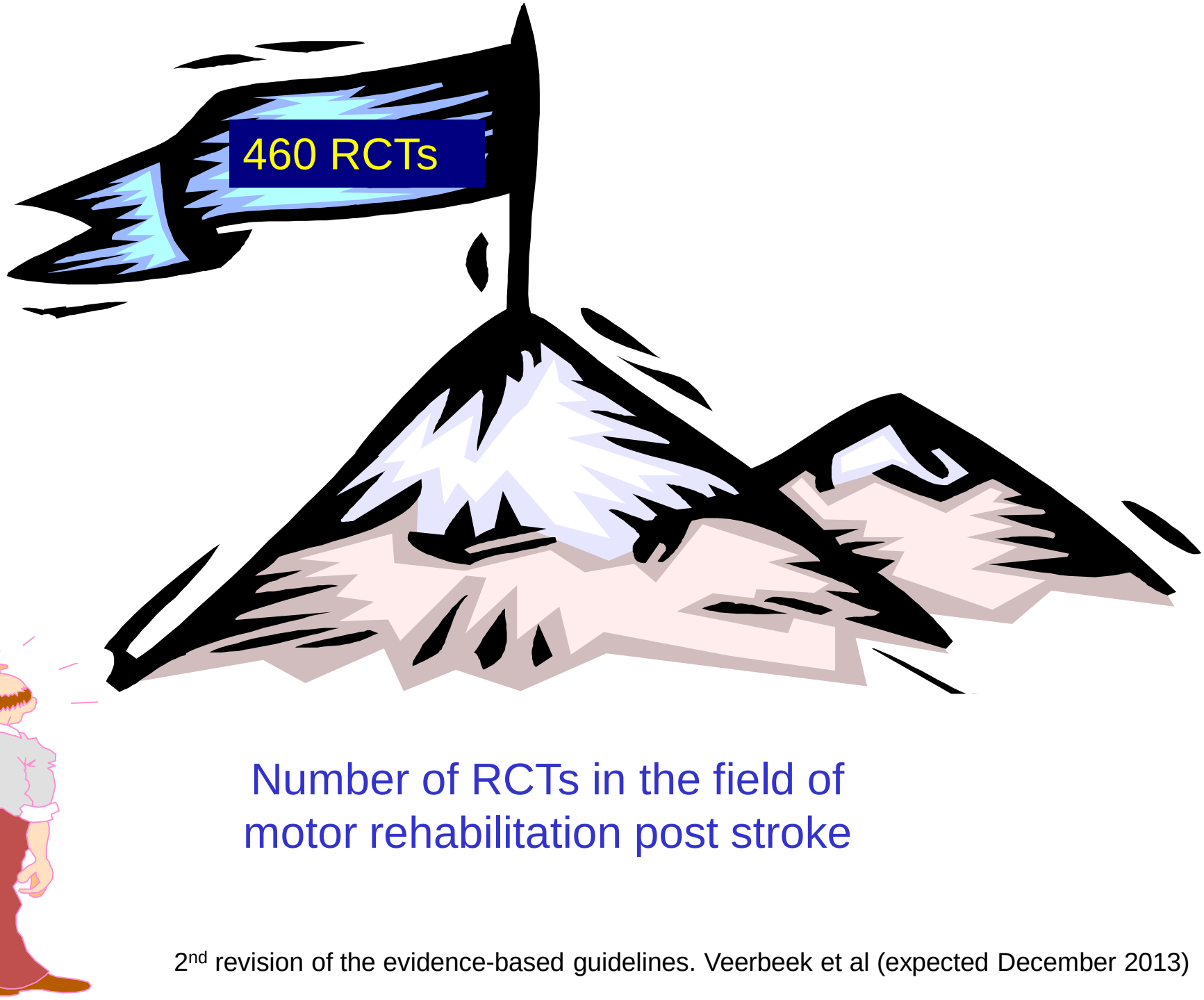
→ **19.977 hits**

→ 153 RCT's / comparisons 1st Dutch stroke guideline '2004'

→ 307 additional RCT's / comparisons at June 2011

→ Total =460 RCT's reflecting ~ 59 different interventions

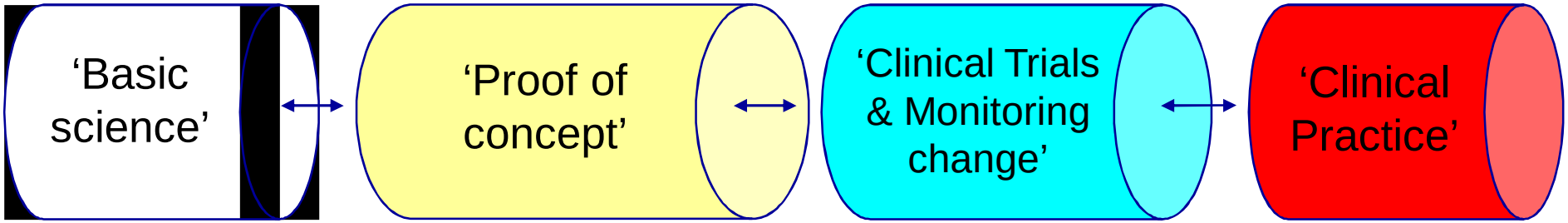
2nd revision of the evidence-based guidelines of the KNGF. Veerbeek et al (expected December 2013)



Number of RCTs in the field of motor rehabilitation post stroke

2nd revision of the evidence-based guidelines. Veerbeek et al (expected December 2013)

'RCTs in domain of rehabilitation after stroke'



- Phase I: Screening for safety
- **Phase II: Establishing the testing protocol (small (mono) centre trials)**

Phase III: Final testing for evidence (large (pragmatic) multicentre trials)

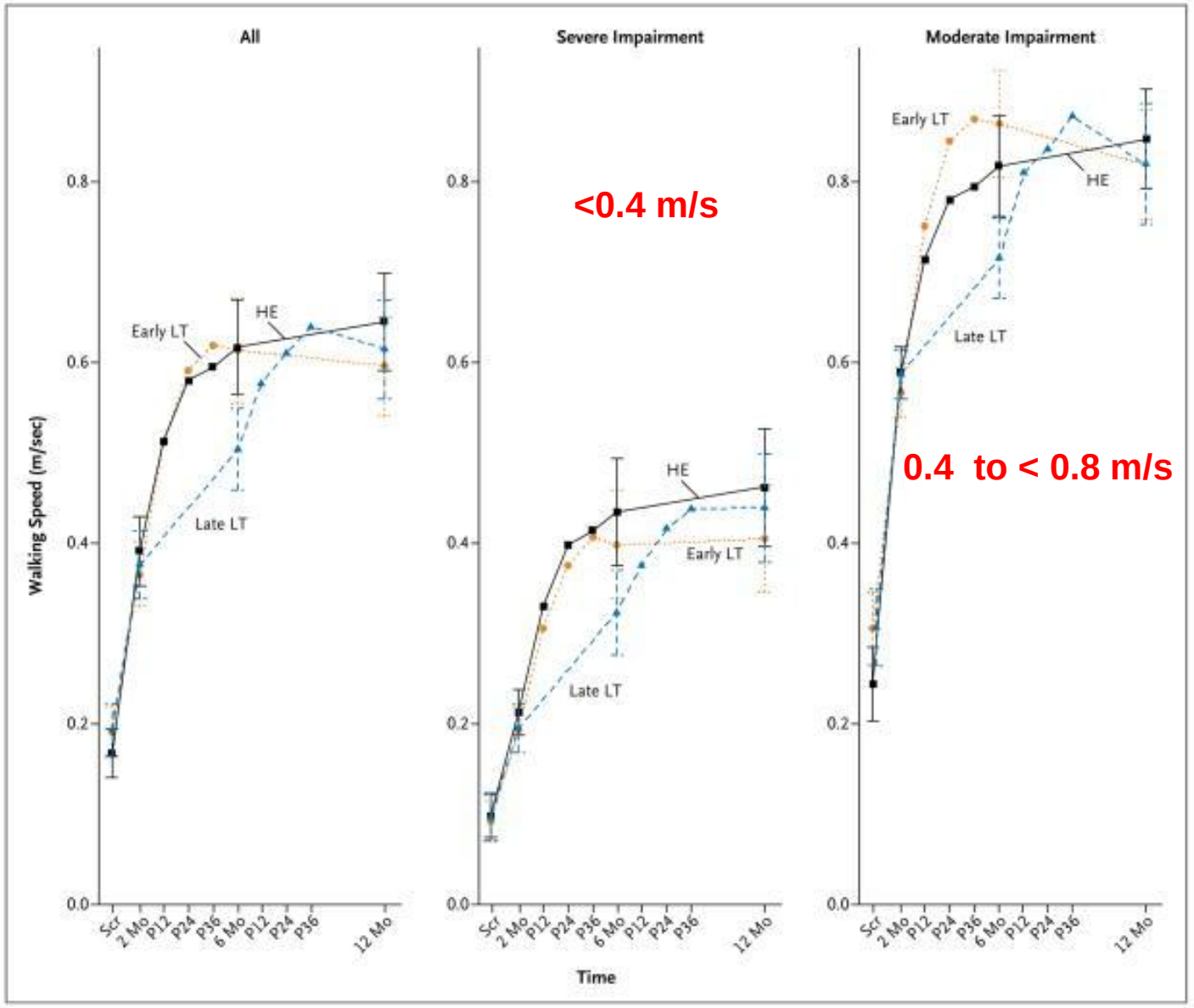
- Phase IV: Post-approval studies (e.g., implementation & cost-effectiveness studies)

Recently published Phase III & IV trials in stroke (2010-2012)

N=408

‘Effects of BWSTT rehabilitation after stroke: The LEAPS trial’. Duncan et al, N Engl J Med. 2011 May 6;364(21):2026-36.

Effects of Body-Weight-Supported Treadmill Training post stroke (N=408).



Duncan PW, et al, N Engl J Med. 2011 May 26;364(21):2026-36.

The NEW ENGLAND JOURNAL of MEDICINE

Recently published Phase III & IV trials in stroke (2010-2012)

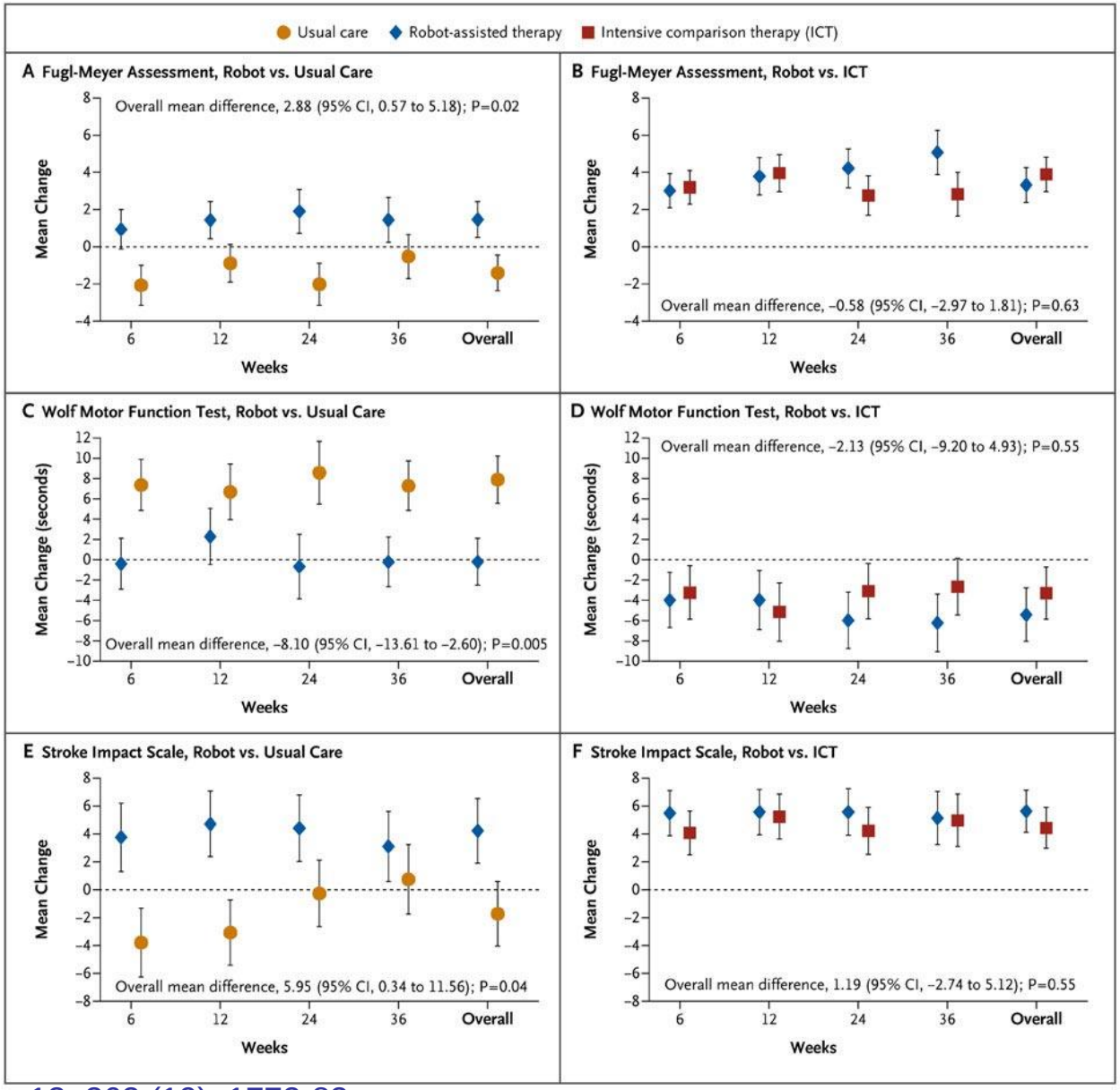
N=408

'Effects of BWSTT rehabilitation after stroke: The LEAPS trial'. Duncan et al, N Engl J Med. 2011 May 6;364(21):2026-36.

N=127

'Robot-assisted therapy for long term upper limb impairments after stroke', Lo et al, N Engl J Med.2010 May13;362(19): 1772-83.

Changes in Primary and Secondary Outcomes during the 36-Week Study Period, as Compared with Baseline



The NEW ENGLAND JOURNAL of MEDICINE

Lo et al. N Engl J Med 2010 May 13; 362 (19): 1772-83

Recently published Phase III & IV trials in stroke (2010-2012)

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N=127

'Robot-assisted therapy for long term upper limb impairments after stroke', Lo et al, N Engl J Med.2010 May13;362(19): 1772-83.

N=250

'Effects of Cicuit Class Training after stroke: The FIT-Stroke trial'. Van de Port et al, BMJ. 2012 May 10;344:e2672.

Circuit Class Training

Balance control

Transfers

8

1

7

2

4-8 patients
&
1-2 staff members

6

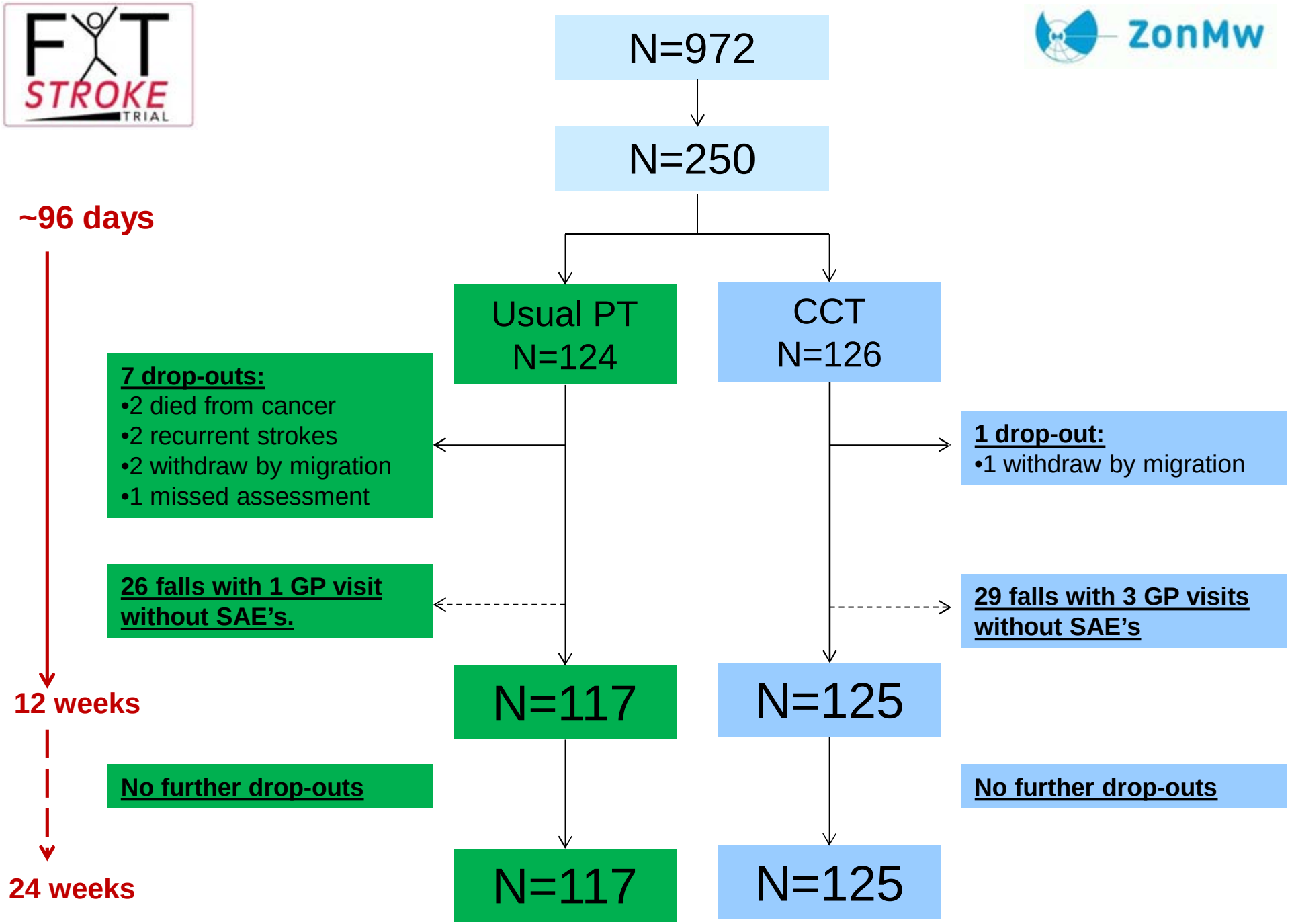
3

5

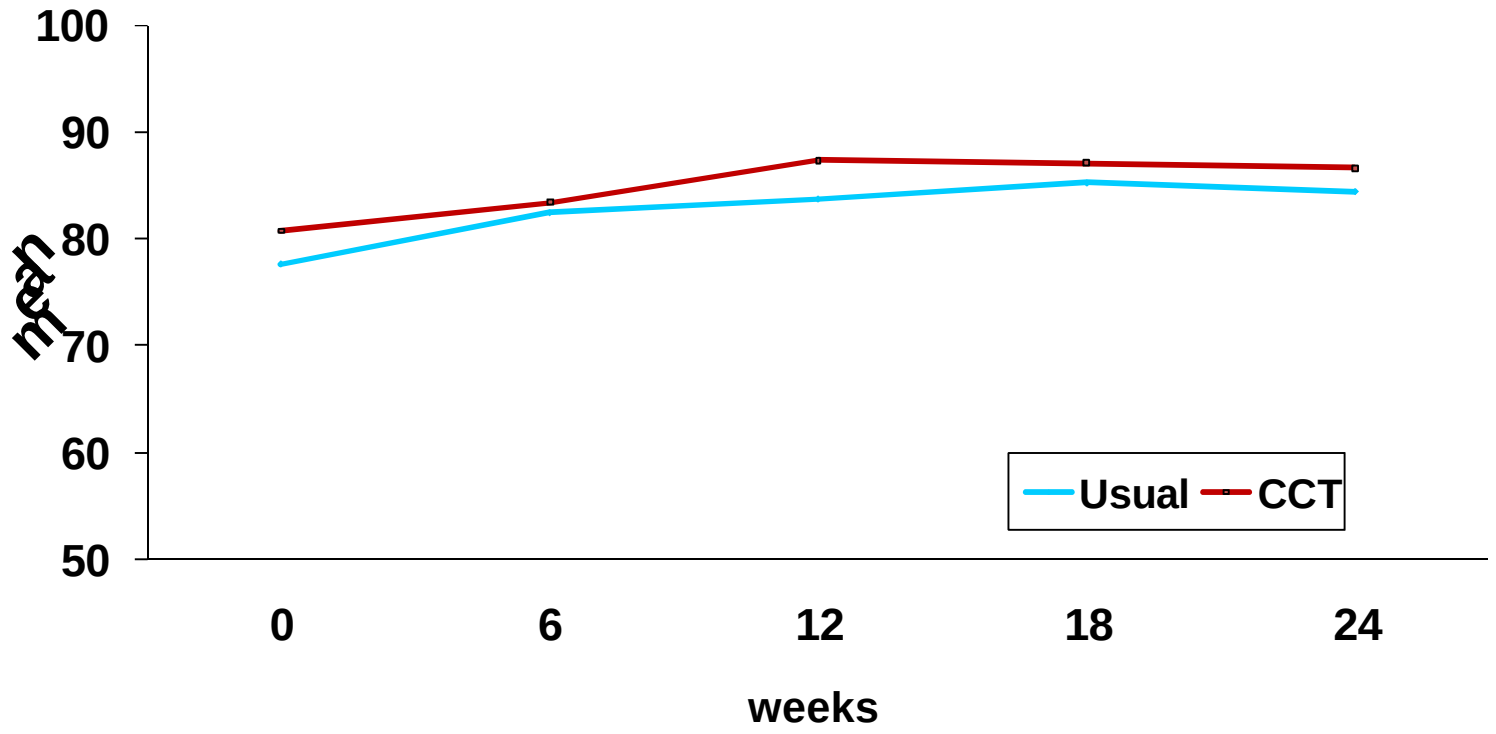
4

Gait performance

Gait-related activities


N=972
N=250
~96 days
Usual PT
N=124
CCT
N=126
7 drop-outs:
•2 died from cancer
•2 recurrent strokes
•2 withdraw by migration
•1 missed assessment
1 drop-out:
•1 withdraw by migration
26 falls with 1 GP visit without SAE's.
29 falls with 3 GP visits without SAE's
12 weeks
N=117
N=125
No further drop-outs
No further drop-outs
24 weeks
N=117
N=125

SIS mobility domain (0-100) (N=250)



- Overall group*time effect: ?=-0.140 (0.138); p=NS
- Overall time effect: ?š 1.656 (0.227); p<0.001
- **Intervention phase: ?=-0.049 (0.682); p=NS**
- Follow up phase: ?ę-0.640 (0.595); p=NS

Recently published Phase III & IV trials in stroke (2010-2012)

N=408

'Effects of BWSTT rehabilitation after stroke: The LEAPS trial'. Duncan et al, N Engl J Med. 2011 May 6;364(21):2026-36.

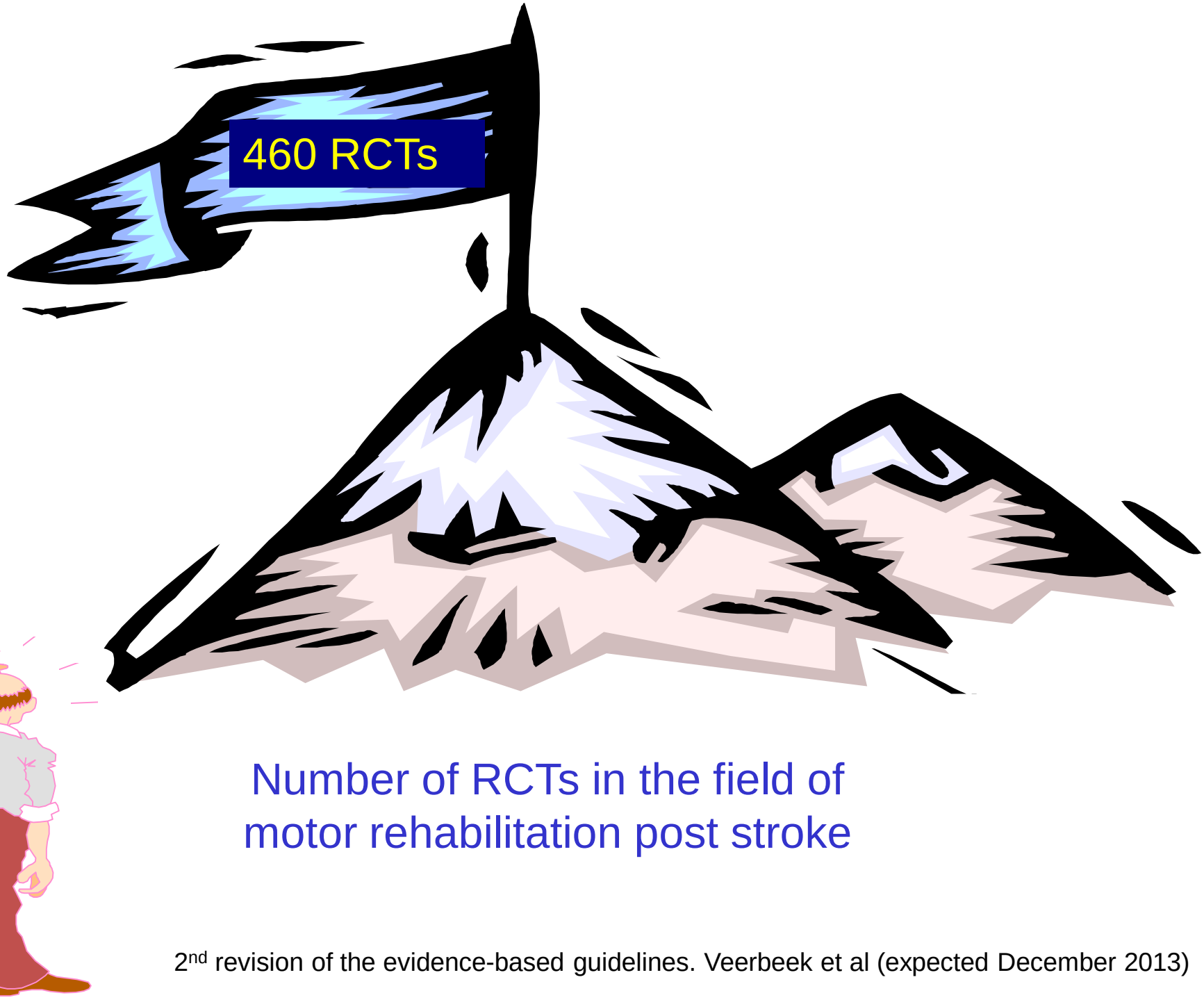
N=127

'Robot-assisted therapy for long term upper limb impairments after stroke', Lo et al, N Engl J Med.2010 May13;362(19): 1772-83.

NEGATIVE TRIALS

N=250

'Effects of Cicuit Class Training after stroke: The FIT-Stroke trial'. Van de Port et al, BMJ. 2012 May 10;344:e2672.



Number of RCTs in the field of motor rehabilitation post stroke

2nd revision of the evidence-based guidelines. Veerbeek et al (expected December 2013)

What are the reasons for the higher proportion positive phase II trials compared to recently phase III and IV trials in neurorehabilitation?

- Better selection of patients in phase II trials when compared to III and IV trials?
- More methodological bias in phase II trials when compared to III and IV?

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PEDro-Scale (n=460 trials)

1. Adequate randomization procedure?
2. **Concealed allocation?**
3. **Comparability of patients groups?**
4. Blinding patients?
5. Blinding therapists?
6. **Blinding observers?**
7. >85% of the sample measured by one key outcome?
8. **Intention-to-treat analyses of at least one key outcome?**
9. **Between-group statistical comparisons are reported for at least one key outcome**
10. The study provides both point measures and measures of variability for at least one key outcome

http://www.pedro.fhs.usyd.edu.au/

Foley CN, Phys. Ther. 2006; 86:817-824

PEDro scores:

- PEDro score <2004 (N=153):
  - Mean (SD): 5.05 (1.46)
  - Median (IQR): 5 (4-6)

- PEDro score 2004-2011 (N=307 trials):
  - Mean (SD): 5.83 (1.50)
  - Median (IQR): 6 (5-7)

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What are the reasons for the higher proportion positive phase II trials compared to recently phase III and IV trials in neurorehabilitation?

- Better selection of patients in phase II trials when compared to III and IV trials?
- More methodological bias in phase II trials when compared to III and IV?
- Reflection of publication bias?
- ???

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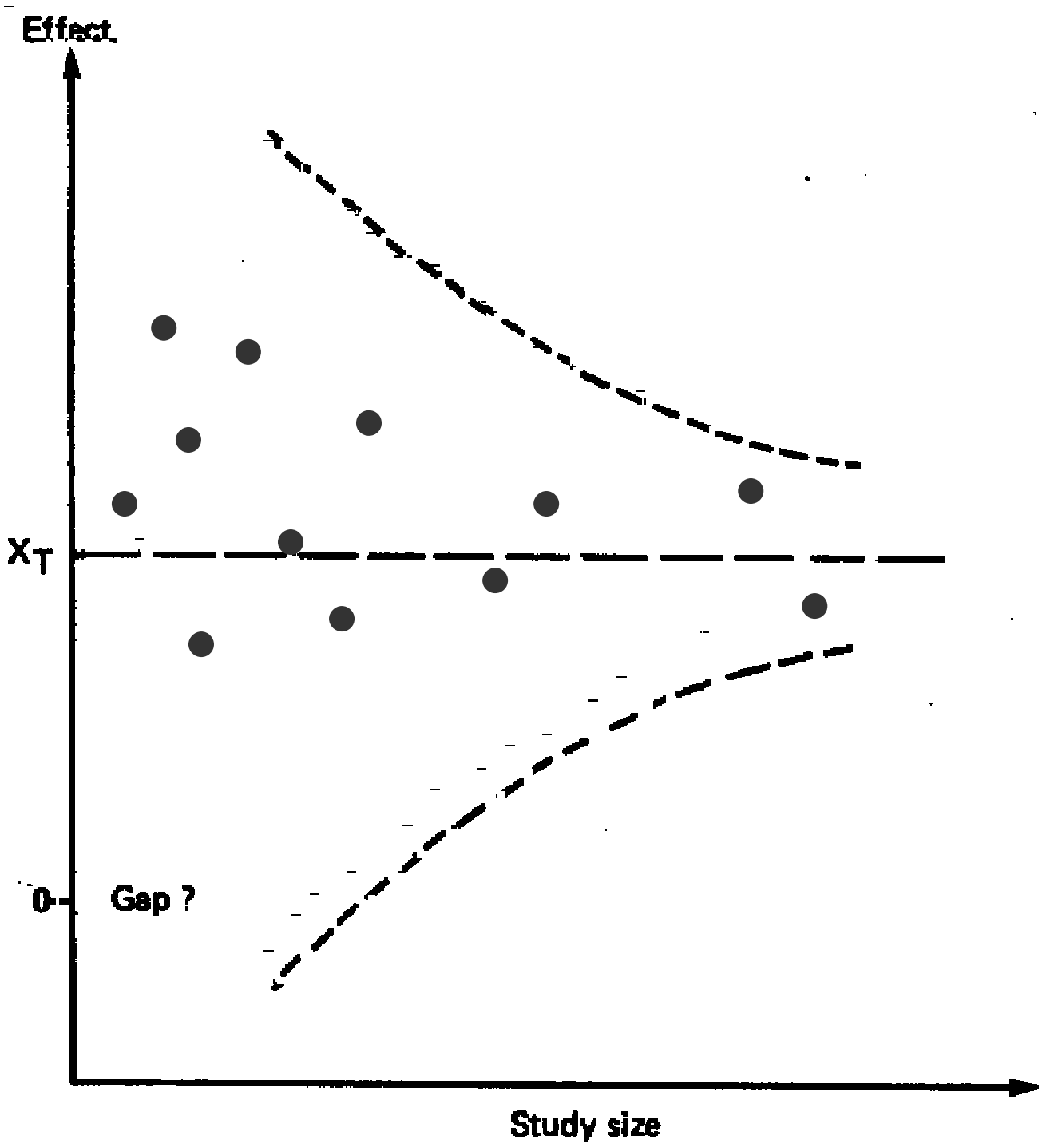

Effect
X_T
0
Gap ?
Study size

My students are dismayed when I say to them:

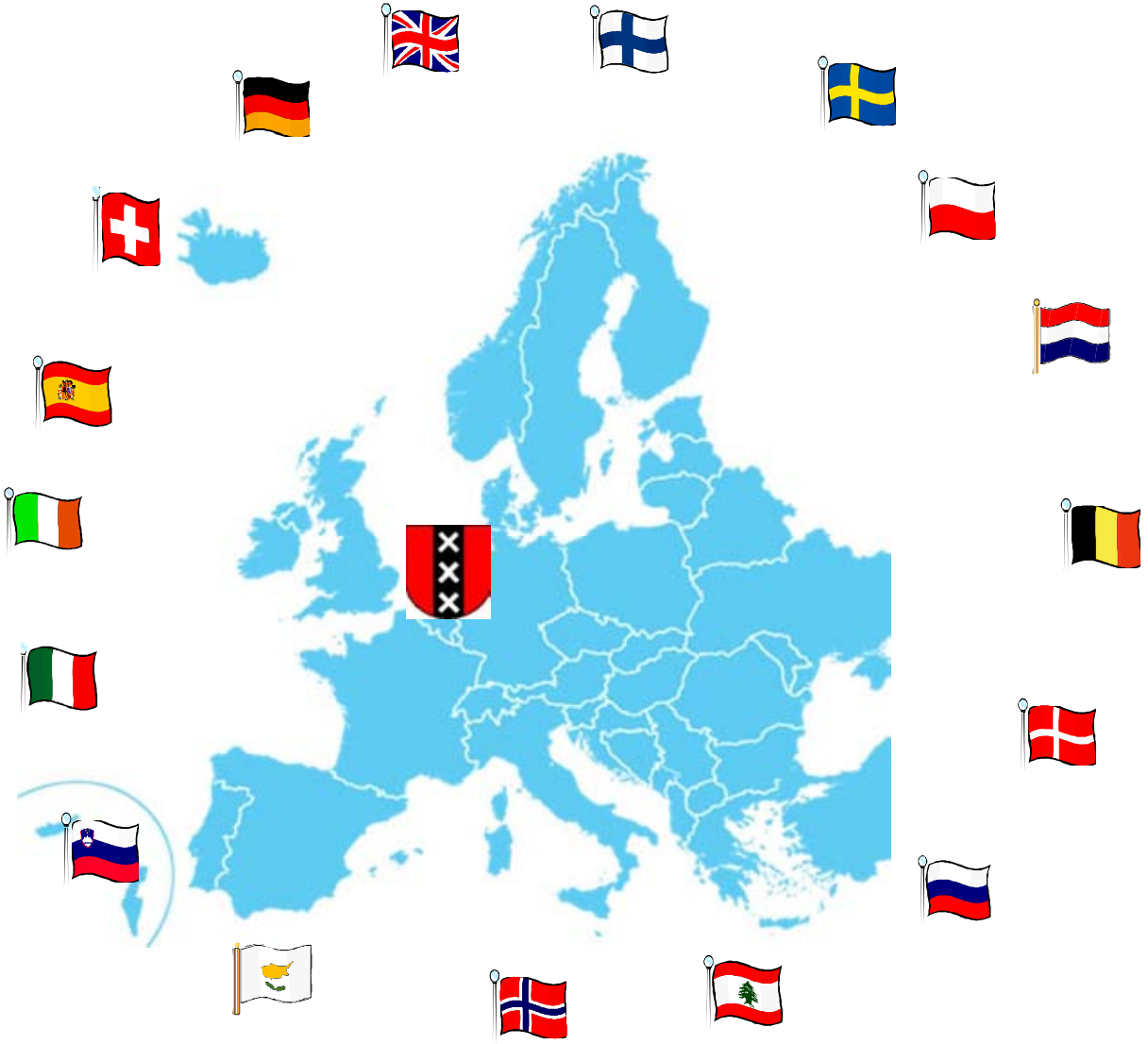
"Half of what you are taught as medical students will in 10 years have been shown to be wrong."

And the trouble is none of your teachers knows which half."

Dr. Sydney Burwell, Dean Harvard Medical School In: Evidence based medicine, Sackett et al, 2000: 31


Revalidatie na een beroerte
Richtlijnen en aanbevelingen voor zorgverleners
National clinical guideline for stroke
Third edition
Incorporating the recommendations from Stroke: national clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA) by the National Institute for Health and Clinical Excellence
Prepared by the Intercollegiate Stroke Working Party
July 2008
GF-richtlijn
Life after stroke
New Zealand guideline for management of stroke
Best practice evidence-based guideline
November 2003
118
Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning
A national clinical guideline
June 2010
Stroke Rehabilitation and Recovery
National Stroke Foundation 2005
UP-TO-DATE GUIDELINES

Stroke [N]Euro-rehab GUIDEline`
(Expected ~December 2013)



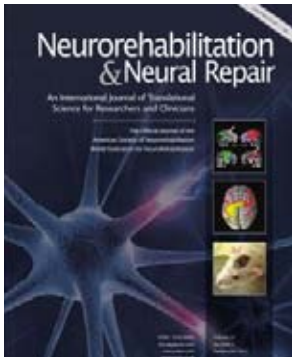
de Fysiotherapeut

Janne Veerbeek, MSc | E j.veerbeek@vumc.nl

DSNR
Dutch Society of Neuro-Rehabilitation

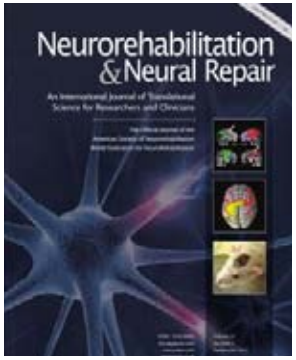
Most common flaws in submitted trials for NNR

- No selection of a primary measurement of outcome
- No correction for multiple testing (ie, Bonferroni correction)
- No definition of a clinically meaningful difference between both treatment arms
- To much emphasis on: 1) within-group analysis
  2) p-values
- Unclearness about the concealment of allocation of randomized subjects.
- Absence of intention-to-treat analyses

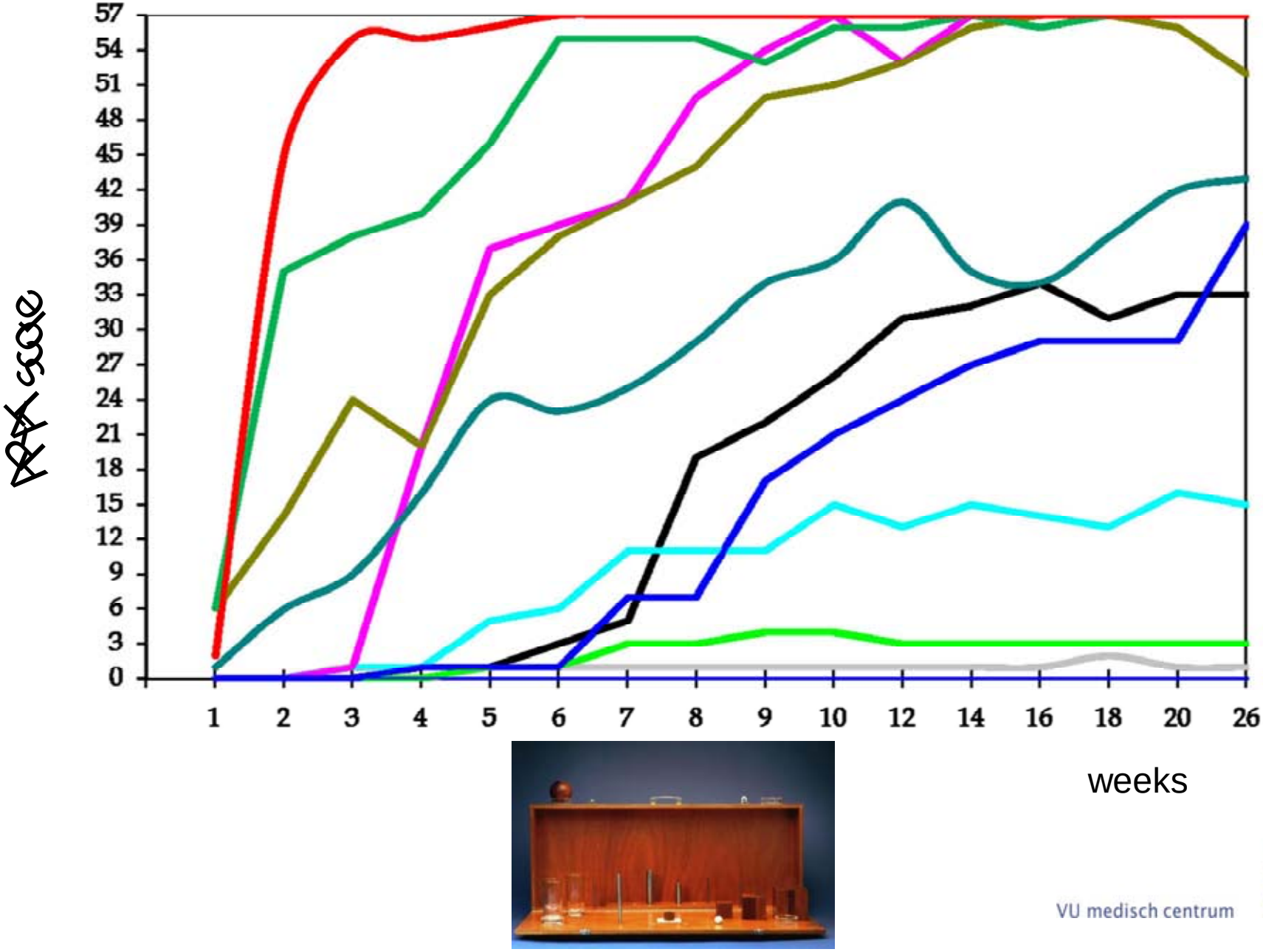


Most common flaws in submitted trials for NNR

- No blinding procedures (of observers) including report of the succes of applied blinding procedures afterwards.
- Unclearness about point measures and estimates of variability of applied outcomes
- Some small trials suffer from inbalances at baseline with respect to most important indicators (in particular for trials of the upper paretic limb)
- Most rehabilitation trials are underpowered with respect to the heterogeneity of (stroke) population of interest.



Who should I select for my trial? (N=10)



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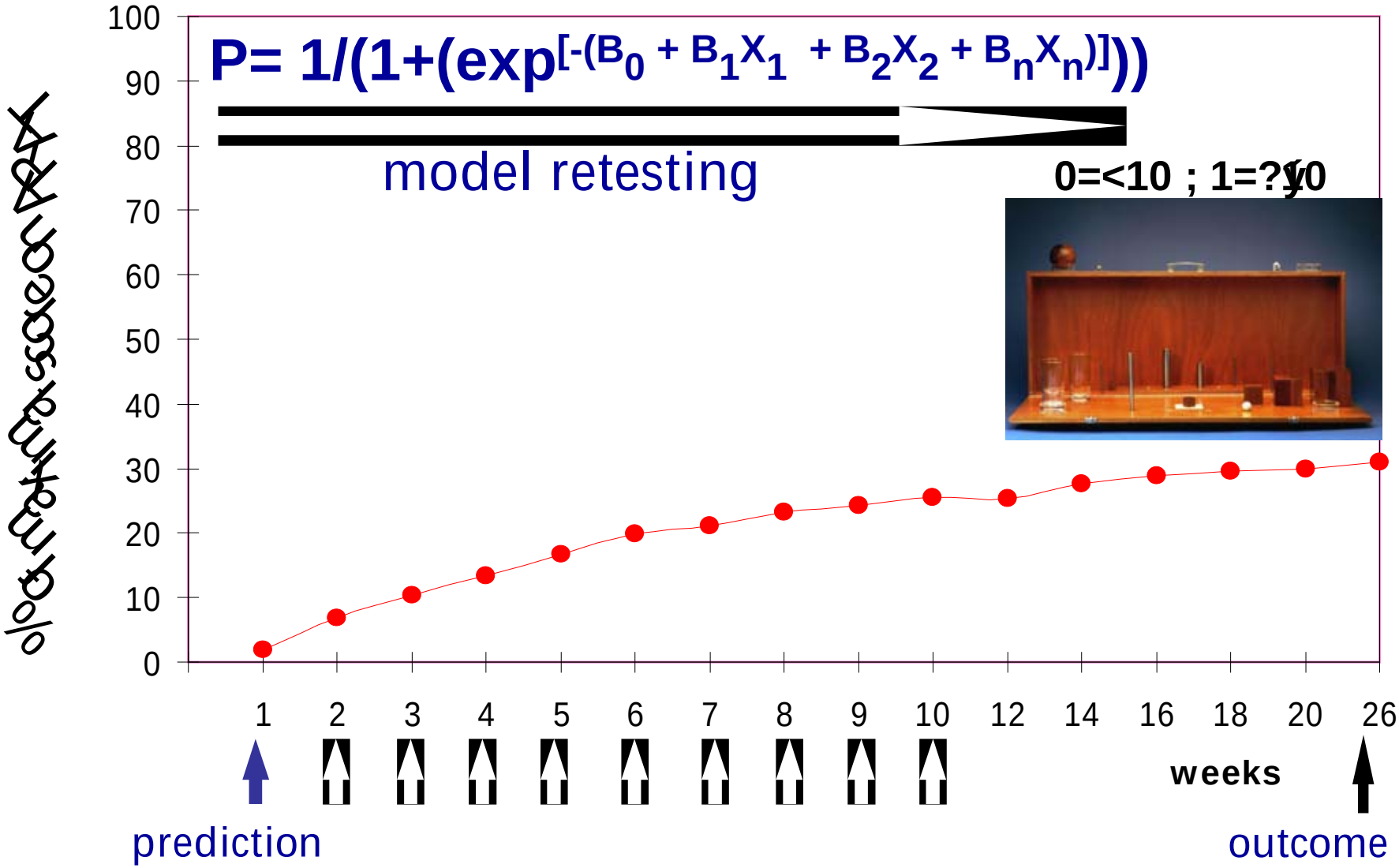
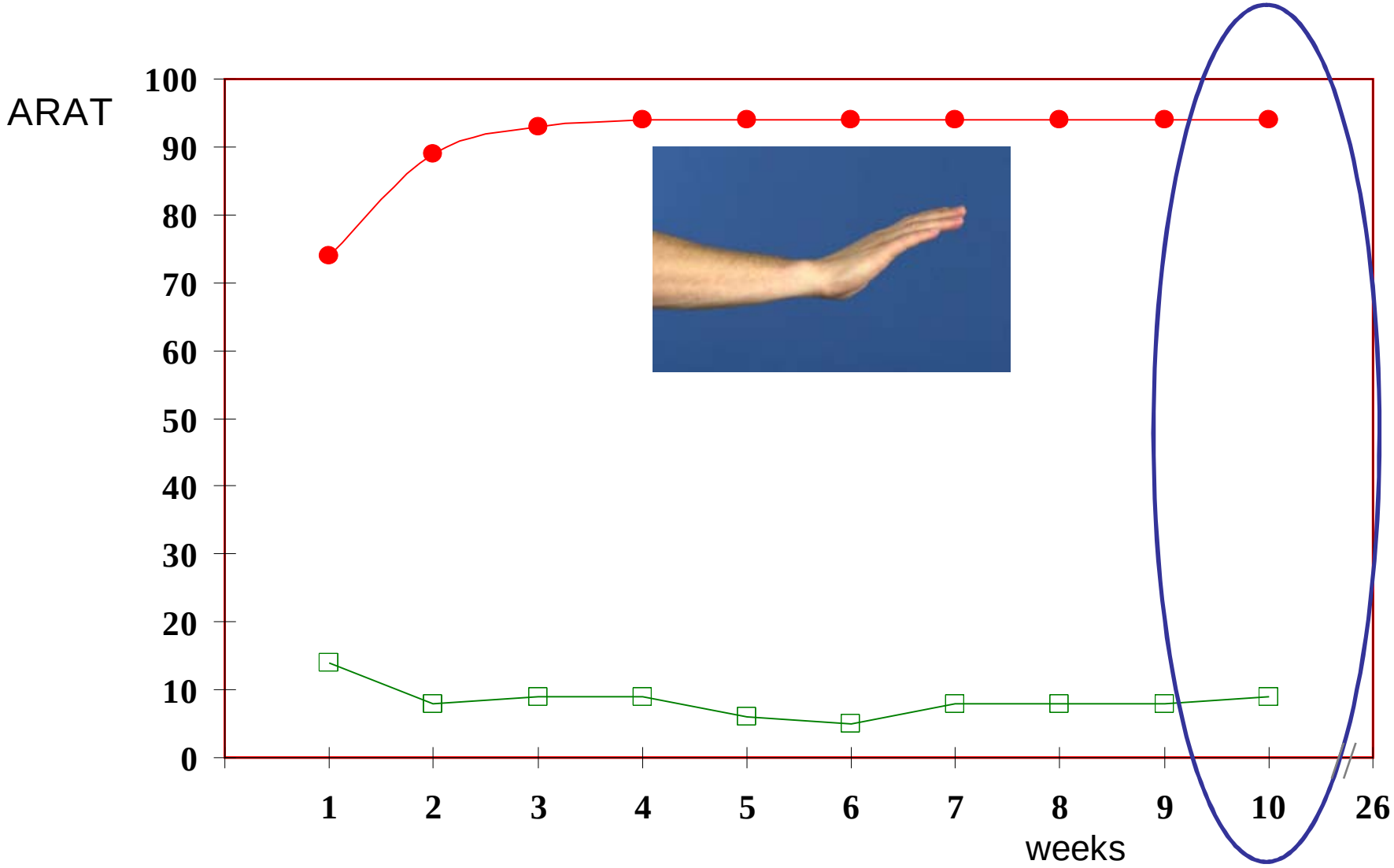
Who should I select for my trial? (N=102)



Kwakkel et al, Stroke 2003; 34: 2181-2186

No pre-selection with respect to wrist and finger extension (N=102)



Kwakkel et al, Neurorehabil Neural Repair. 2008;22(2):111-21

Sample calculation for a two arm RCT of the upper paretic limb with ARAT as primary outcome measure (1):

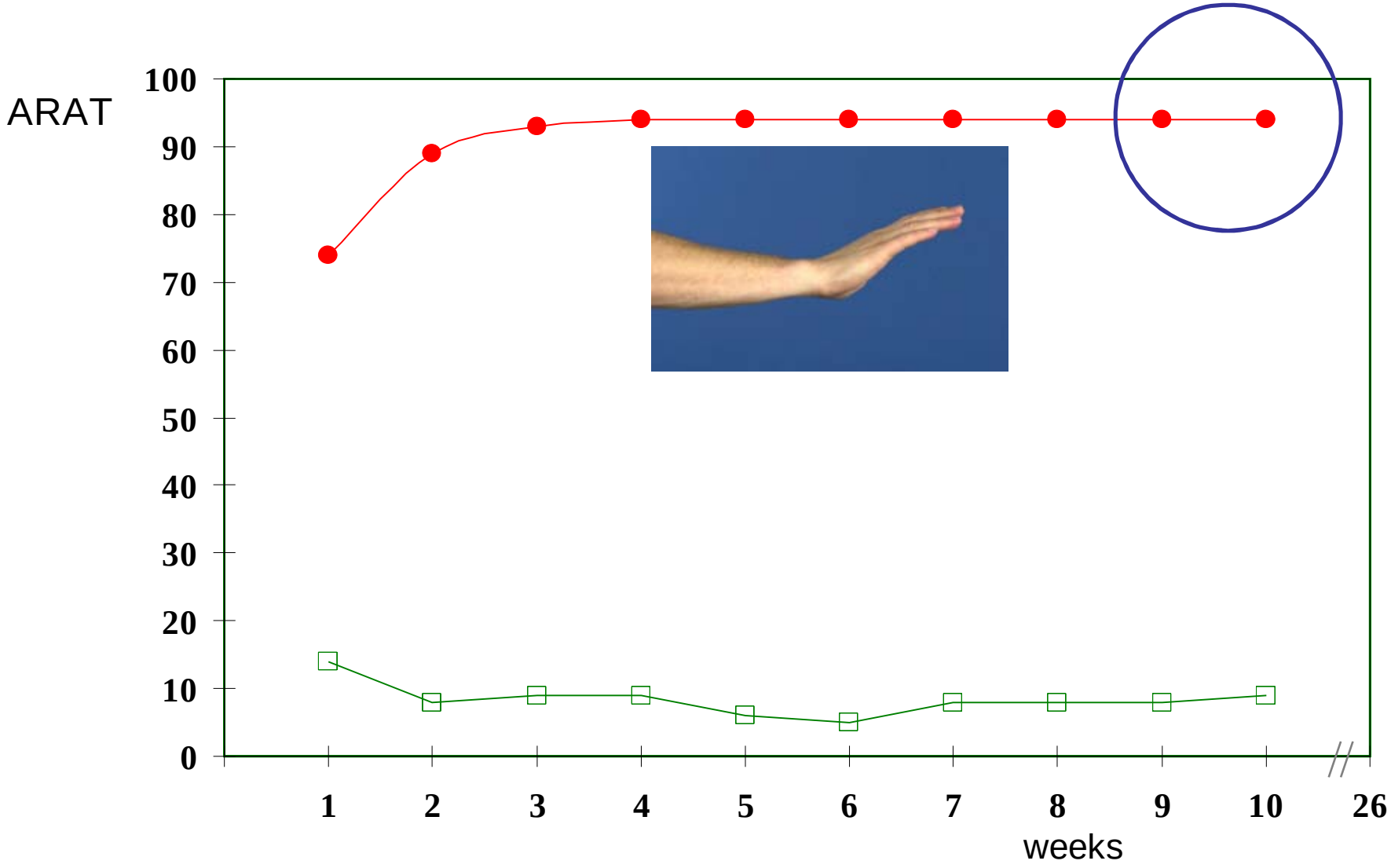
Power calculation (unrestricted sample at 10 weeks post stroke):

- $(Z_{1-\beta})$: 80% power = 0.84
- $(Z_{1-\alpha})$: 5% = 1.96
- σ = 32 points (non-stratified)
- MCID on ARAT=6 points ~10%

$$N_{\text{per arm}} = \frac{2 \times (Z_{1-\alpha} + Z_{1-\beta})^2 \times \sigma^2}{(\mu_{(exp)} - \mu_{(con)})^2} \Rightarrow N = 47$$

Kwakkel et al, Neurorehabil Neural Repair. 2008;22(2):111-21

Pre-selection on the basis of wrist and finger extension (N=102)



Kwakkel et al, Neurorehabil Neural Repair. 2008;22(2):111-21

Sample calculation for a two arm RCT of the upper paretic limb with ARAT as primary outcome measure (2):

Power calculation (restricted sample at 10 weeks post stroke):

- $(Z_{1-\alpha})$: 80% power = 0.84
- $(Z_{1-\alpha/2})$: 5% = 1.96
- σ = 12 points (stratified to >9 points)
- δ = MCID (=SDD) on ARAT = 6 points

$$N_{\text{per arm}} = \frac{2 \times (Z_{1-\alpha} + Z_{1-\beta})^2 \times \sigma^2}{(\mu_{(exp)} - \mu_{(con)})^2} \Rightarrow N = 63$$

Kwakkel et al, Neurorehabil Neural Repair. 2008;22(2):111-21

How to increase statistical power of trials?

$$N_{eff} = \frac{(Z_{1-\alpha} + Z_{1-\beta})^2 \times \sigma^2 \times (r + 1) \times \{1 + (T-1) \times \rho\}}{(\mu_{exp} - \mu_{con})^2 \times r \times T}$$

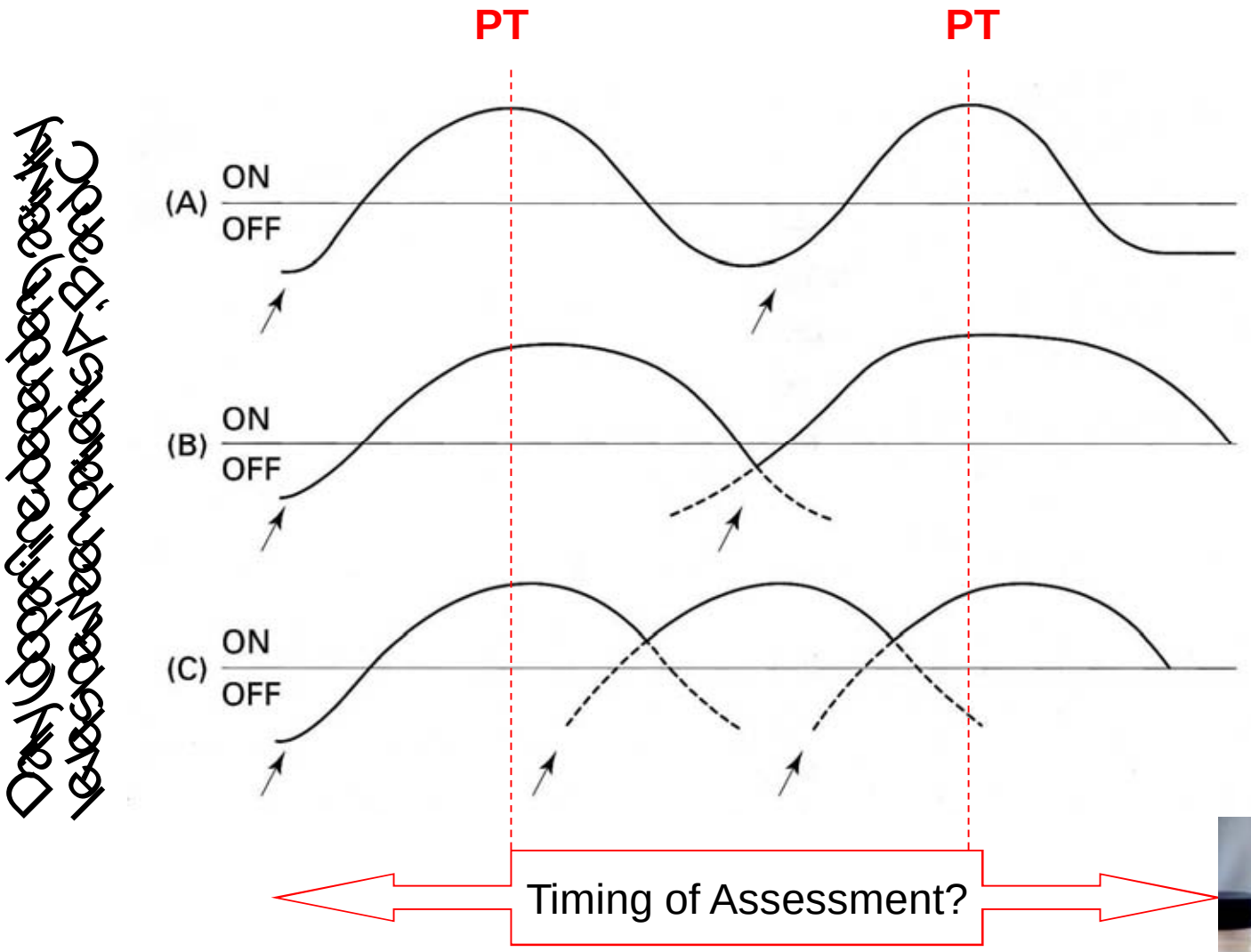
N= Number of patients involved per arm
reducing efficacy of control treatment
$(Z_{1-\alpha} + Z_{1-\beta})^2$= values for correct rejecting H_0 or accepting H_1 hypothesis
σ^2= estimated (population) variance of measurement of outcome
r= ratio between included number of both groups
T= number of follow-up measurements
ρ= within-subject correlation coefficient

‘Using (rhythmic) cues’

RESCUE
Improving mobility for people with Parkinson's disease

Nieuwboer J et al Neurol Neurosurg Psychiatry. 2007 Feb;78(2):134-40.

On / Off phenomena in patients with PD



Nieuwboer et al Neurol Neurosurg Psychiatry. 2007 Feb;78(2):134-40.

Some take home messages (1)

- Evidence of neurorehabilitation is dominated by underpowered trials. A number of these trials suffer from methodological flaws and evidence is probably influenced by publication bias.
- However, there is improvement in methodological quality by increasing awareness of possible shortcomings in trials.
- Need for landmark (phase III) and cost-benefit (phase IV) trials of sufficient methodology and statstical power in neurorehabilitation.
- Need for free access of treatment protocols of applied experimental interventions allowing to replicate their findings.

Some take home messages (2)

- Need for information about the content and intensity of treatment in the control arm (i.e., usual care group) of the trial.

- Need for worldwide consensus on used outcomes (i.e., core sets) in neurorehabilitation trials.

- Need for free access to a web-based ‘up-to-date’ rehabilitation guidelines in which new evidence is continuously added.

- Need for further translational research in neurorehabilitation to improve our existing biological concepts about motor learning and cognition in neurological diseases.

Thank you for your attention!

www.neurorehab.nl

European Research Council

Established by the European Commission

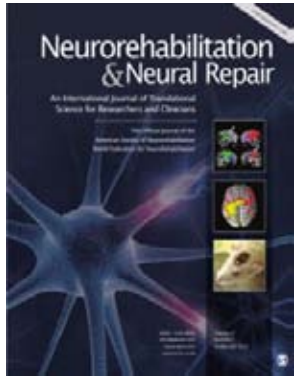
VU rVU medisch centrum

Key problems in most phase II trials

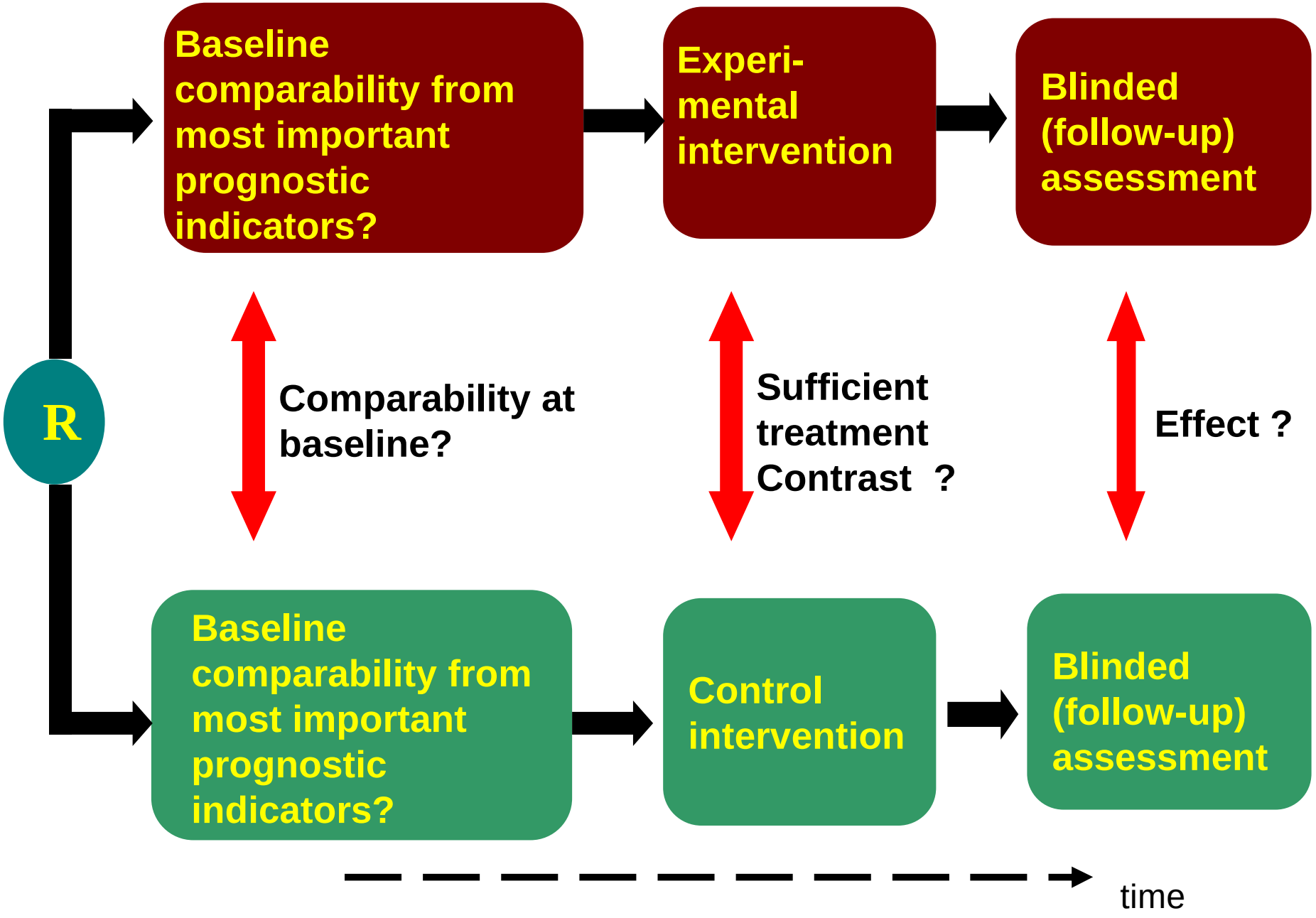
Sample → Definition sample of interest → Baseline measures → R

- § Inclusion-/exclusion criteria
- § Informed consent and rules of good clinical practice

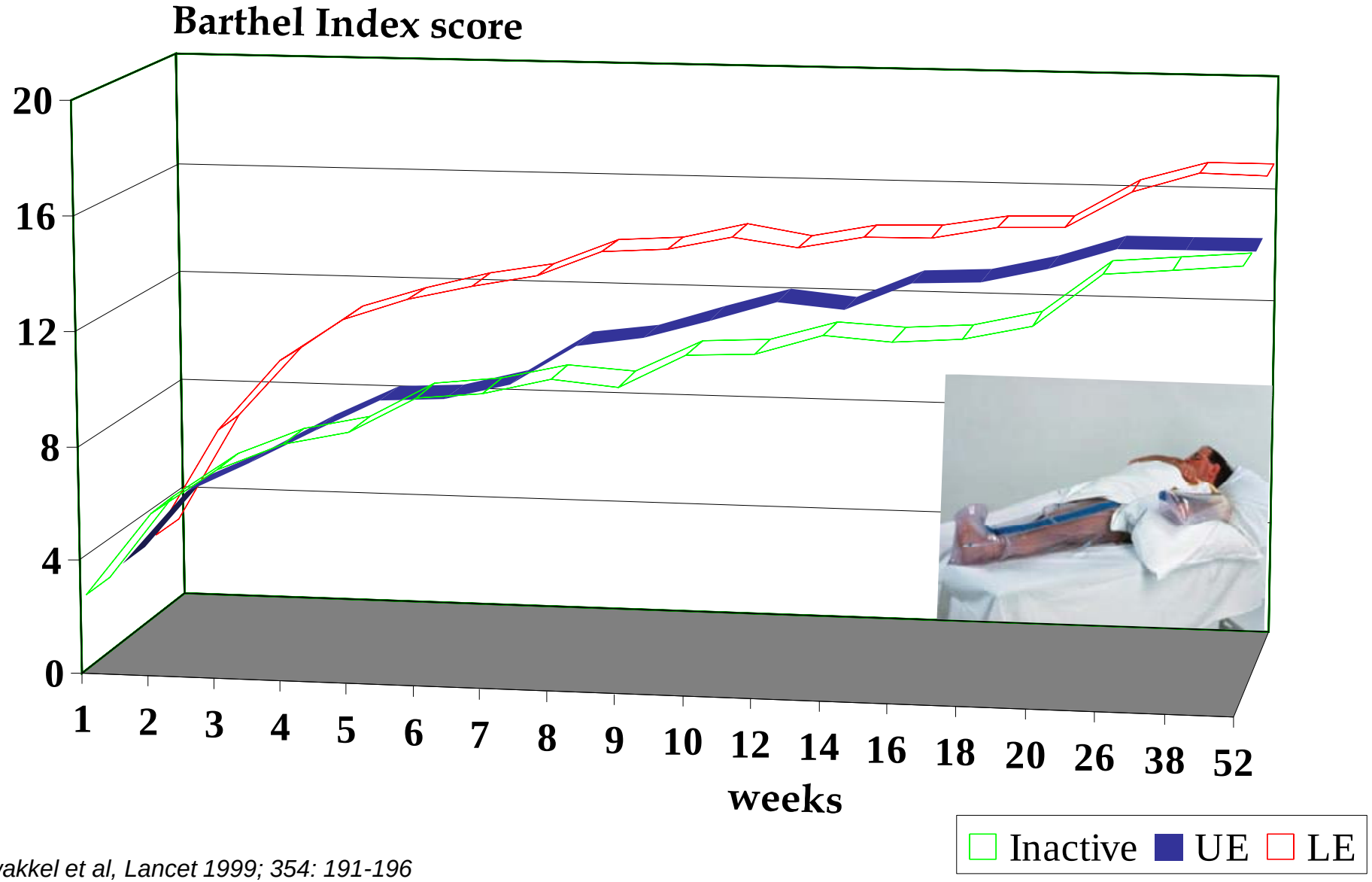
- §Primairy and secondary outcomes defined?
- §Definition of a meaningful difference?



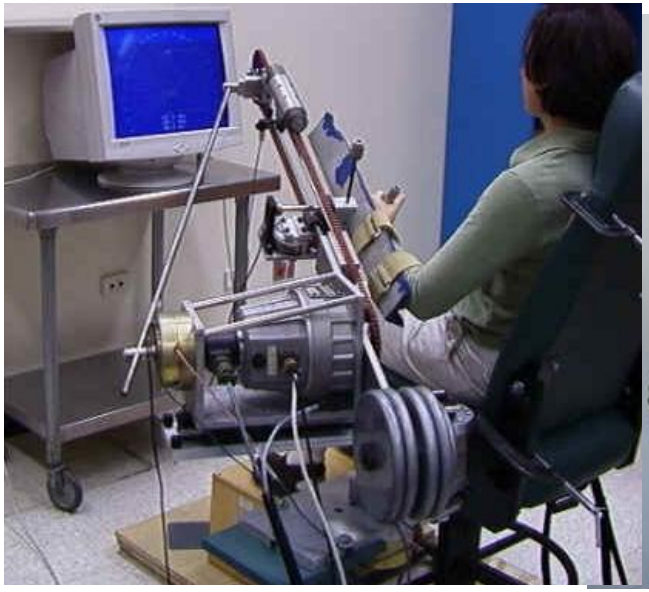
http://www.trialregister.nl/trialreg/index.asp



Effects of intensive task-oriented upper and lower limb training (N=101)



Kwakkel et al, Lancet 1999; 354: 191-196



Arm Guide

MIT-MANUS

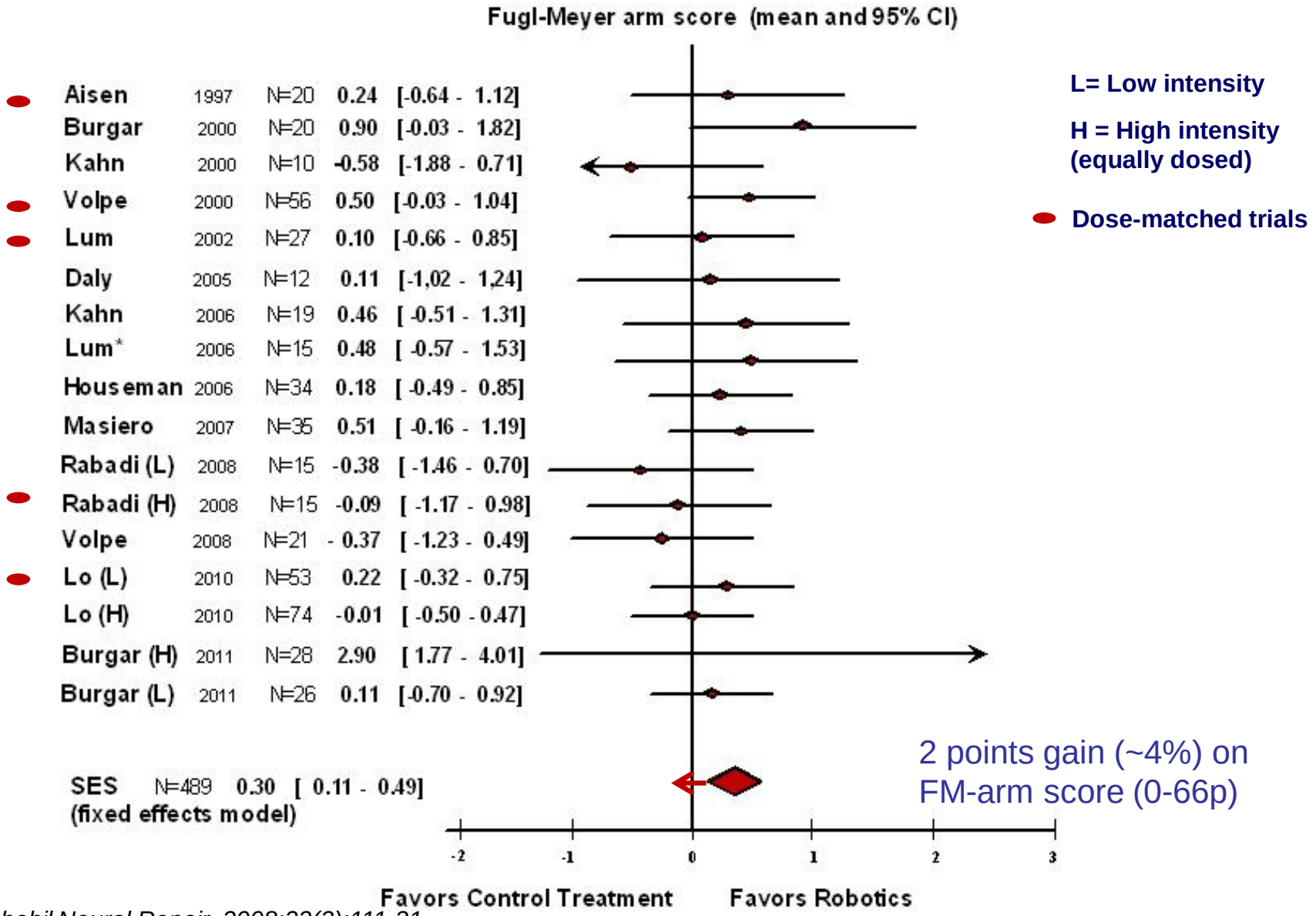
InMotion Shoulder Arm

Bi-Manu Track

ARMin-Robot

MIME

Effects of shoulder-elbow robotics for the upper paretic limb



Neurorehabil Neural Repair. 2008;22(2):111-21

Phases in Neurorehabilitation Trials

- In Phase 1 trials, researchers test an experimental treatment in a small group of people (20–80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

- In Phase 2 trials, the experimental treatment is given to a larger group of people (100–300) to see if it is effective and to further evaluate its safety.

- In Phase 3 trials, the treatment is given to large groups of people (1,000–3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.

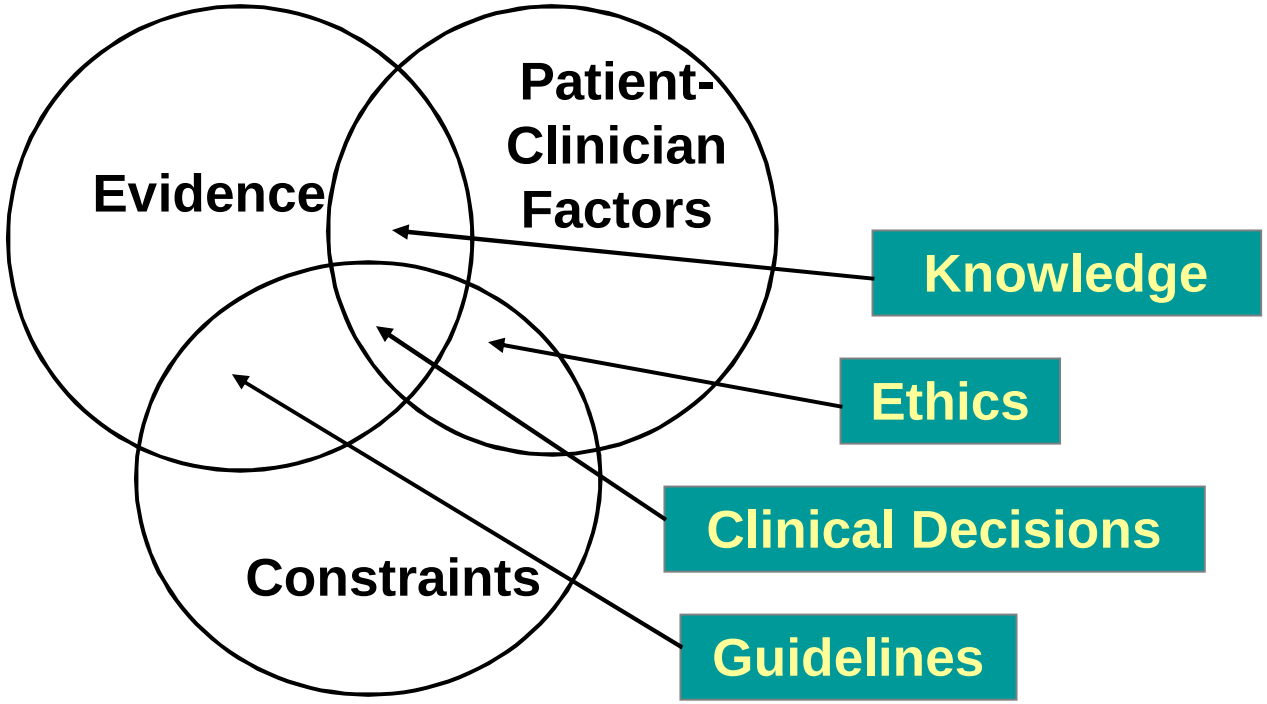
- In Phase 4 trials, postmarketing studies delineate additional information, including the treatment's risks, benefits, and optimal use.

What are the main concerns of trials conducted in stroke rehabilitation?

- Lack of dose-response trials in which the same type of therapy is applied
- Lack of treatment contrast between experimental and control group.
- Lack of RCTs started in the (sub)acute phase post stroke (ie, 3 out of 460 trials did start within days post stroke)
- Over 95% of all trials are small underpowered (ie, phase II trials)
- Many phase II trials suffer from methodological flaws, however improvement in methodological quality is found

Evidence Based Practice and the Real World

- Applying ‘hard’ evidence to practice setting
- Other elements entering clinical decisions:



Point: Evidence is only one element in a complex set of relationships

Davidoff, 1999, Mt Sinai J Med

Some take home messages

- Intensity and task-specificity are the main drivers of motor rehabilitation, however dose-response trials are lacking in the literature.
- Benefits of most rehabilitation interventions are conditional and require knowledge about functional prognosis. (Who should I select?)
- Need for dose-response trials in which the same type of therapie is applied.
- Need for landmark (phase III) and cost-benefit (phase IV) trials with sufficient methodology and statstical power
- Need for world wide consensus on used outcomes and algorithms for applying rehabilitation interventions.
- Need for free access to a web-based up-to-date rehabilitation guidelines

Some take home messages

- Intensity and task-specificity are the main drivers of motor rehabilitation, however dose-response trials are lacking in the literature.
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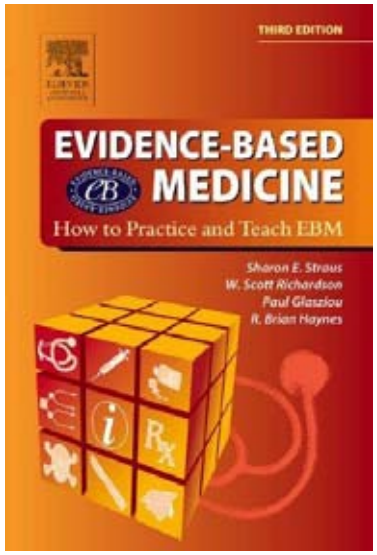
Other problems in rehabilitation trials

- There is often unclearness about the exact treatment protocol that is applied in the RCTs
- Unclearness about the treatment applied in the control group (eg, ‘usual care’, ‘conventional treatment’)
- Unclearness about the number of phase II trials that are negative and not accepted for publication scientific peer reviewed journals.
- No worldwide consensus on using a core set of outcomes allowing comparison between trials in meta-analyses.
- The liteature suffers from ’*novelty effects*’ (ie, ‘innovative interventions with positive effects are more likely to be published’

Evidence-based medicine (EBM) is the *integration* of the best research evidence with our *clinical expertise* and our *patient's unique values* and *circumstances.*



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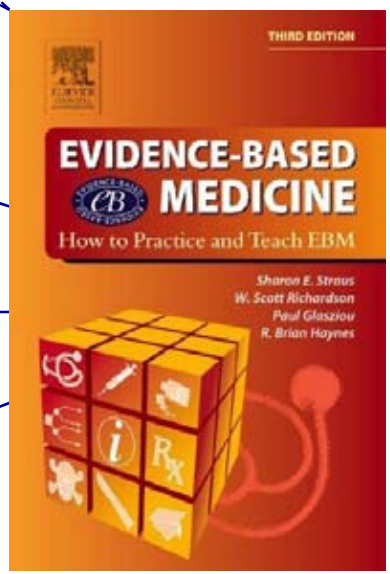
Identify patient's problem

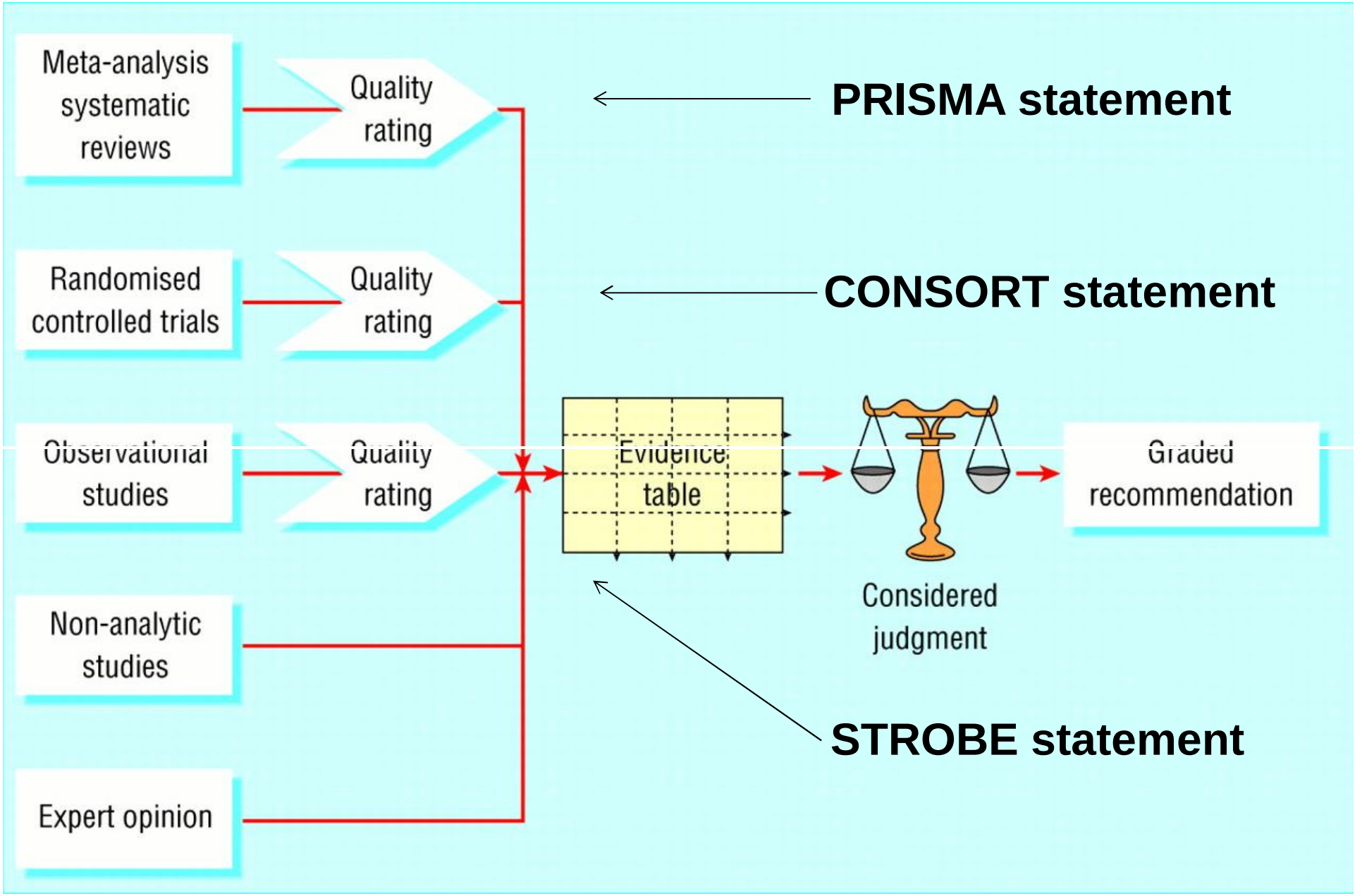
Formulate a clinically relevant question

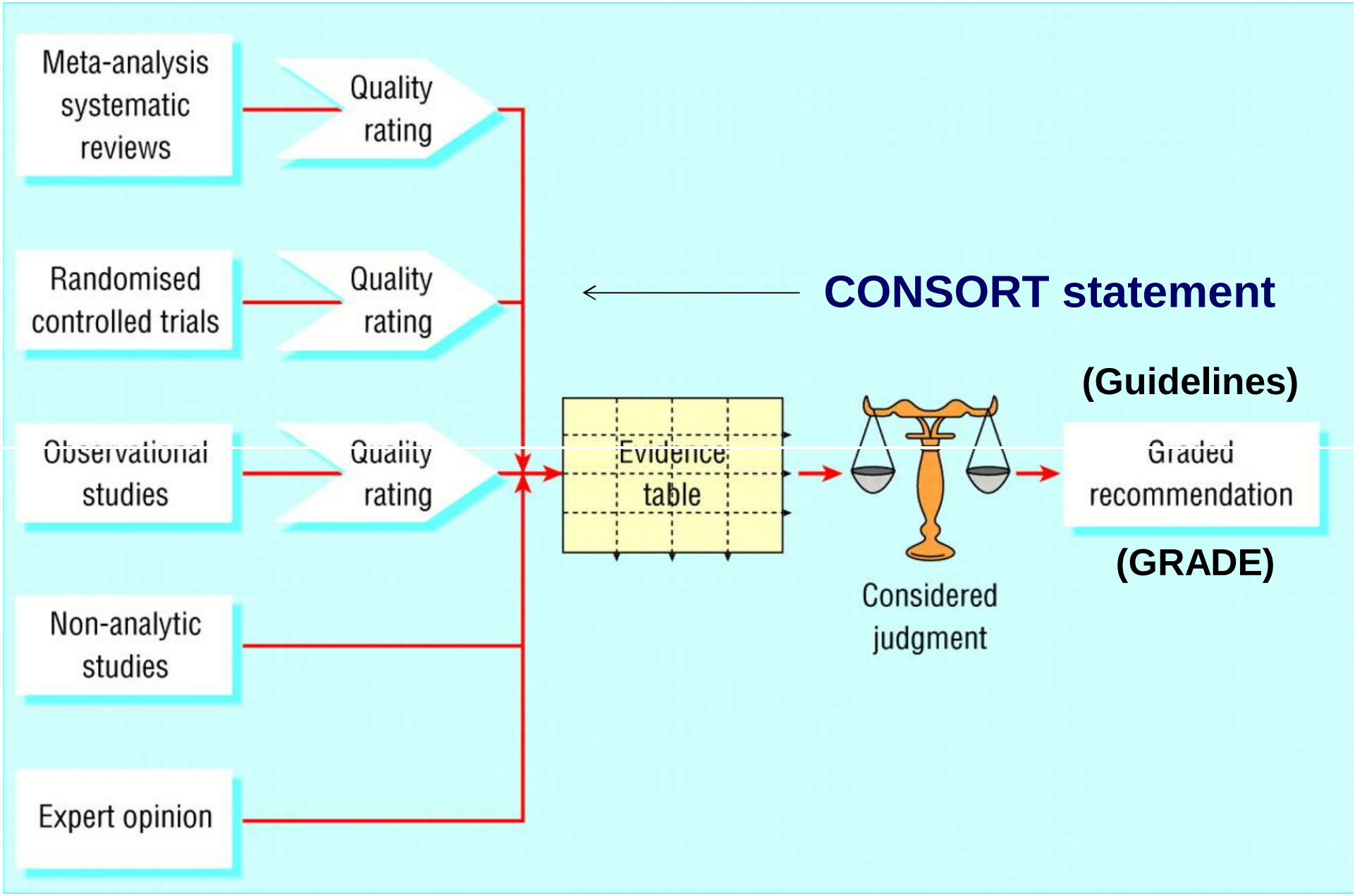
Make a valid (functional) prognosis

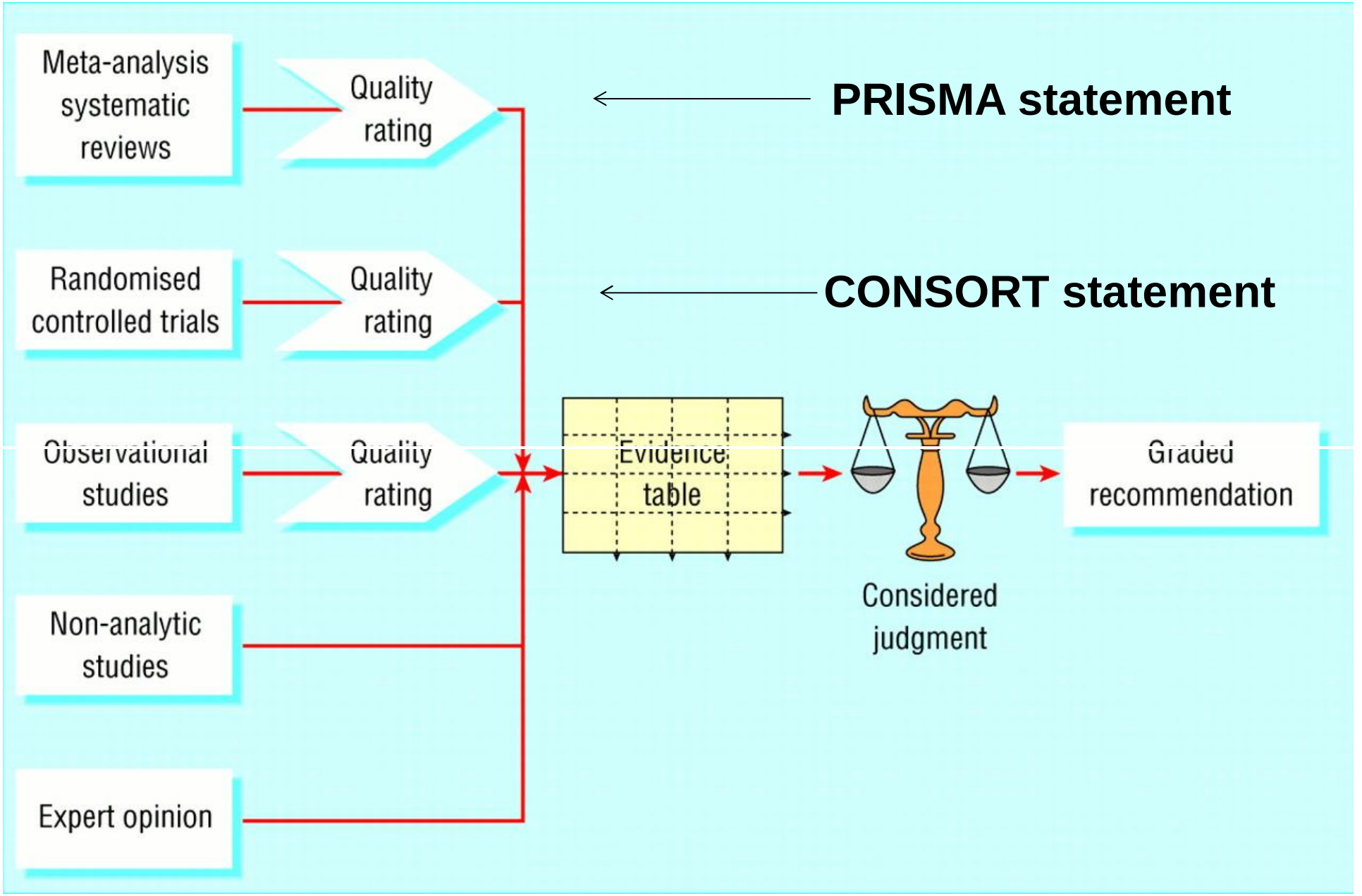
Select the most appropriate therapy

Evaluate outcome with valid measurements




Meta-analysis systematic reviews
Quality rating
Randomised controlled trials
Quality rating
Observational studies
Quality rating
Non-analytic studies
Expert opinion
Evidence table
Considered judgment
Graded recommendation
PRISMA statement
CONSORT statement
STROBE statement


Meta-analysis systematic reviews
Quality rating
Randomised controlled trials
Quality rating
Observational studies
Quality rating
Non-analytic studies
Expert opinion
CONSORT statement
(Guidelines)
Evidence table
Considered judgment
Graded recommendation
(GRADE)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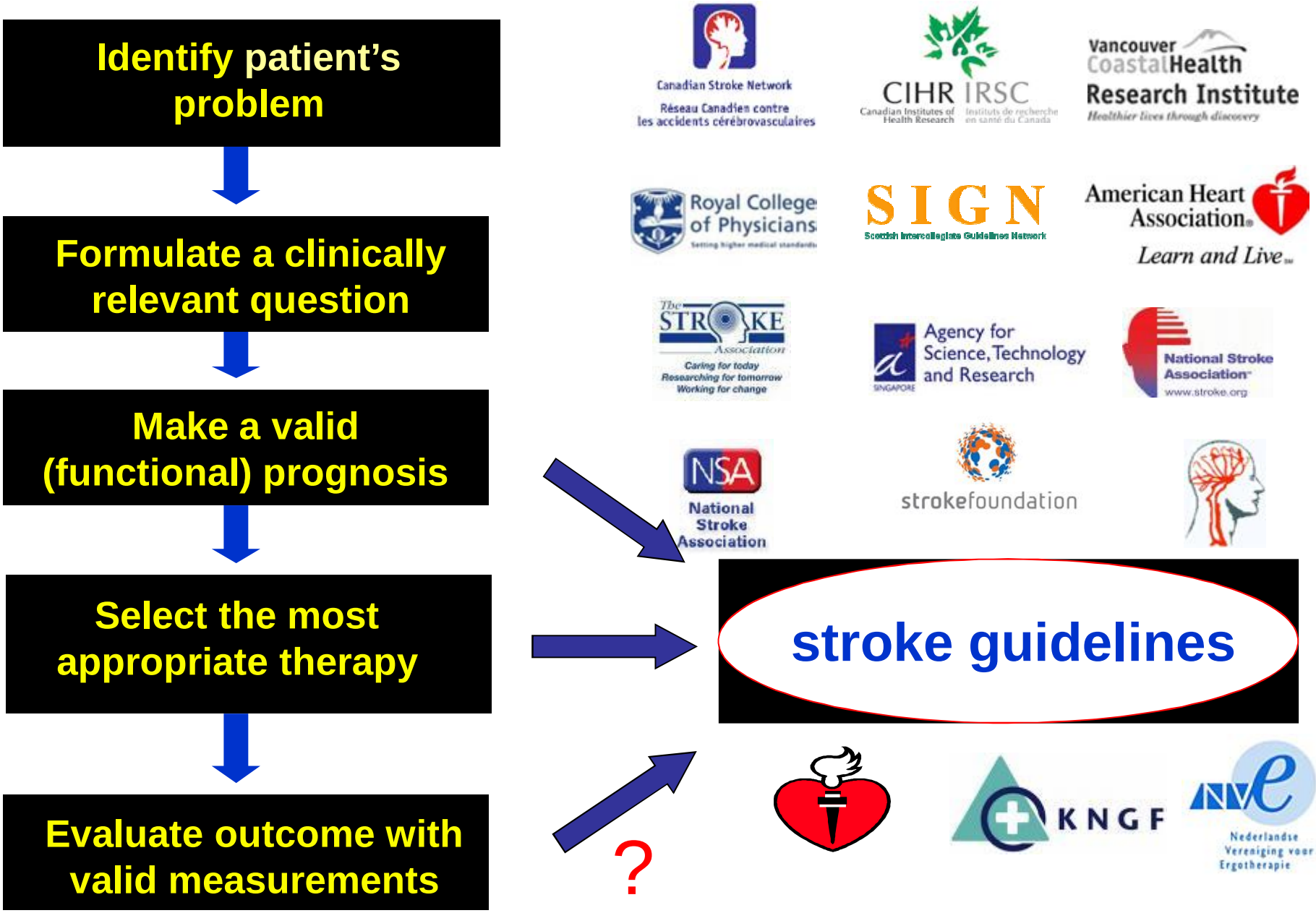
Identify patient's problem
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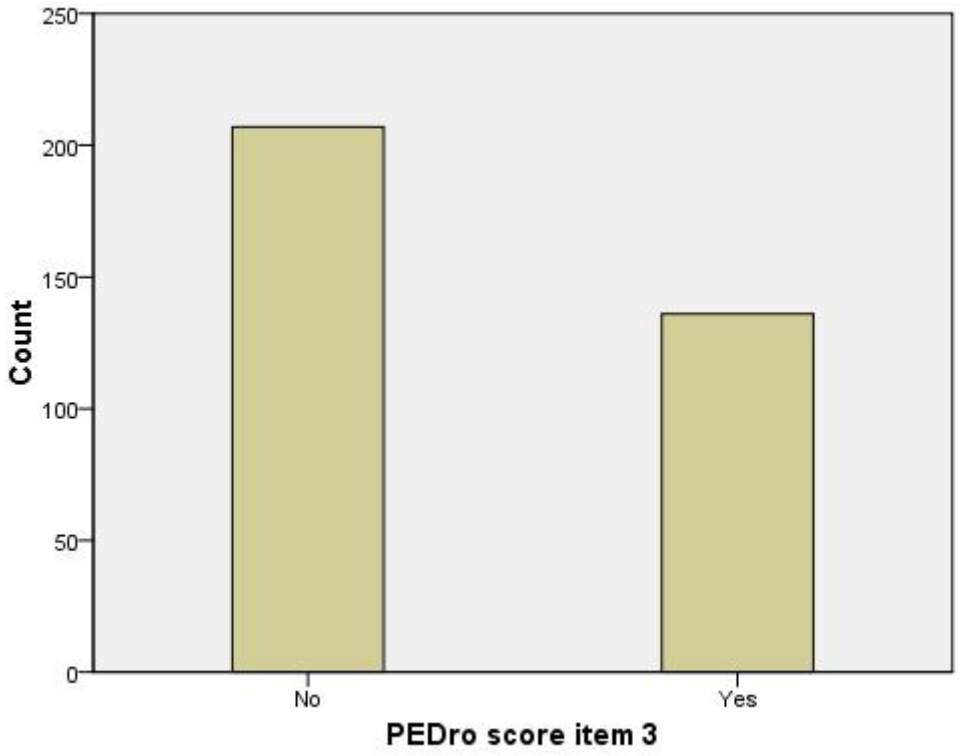
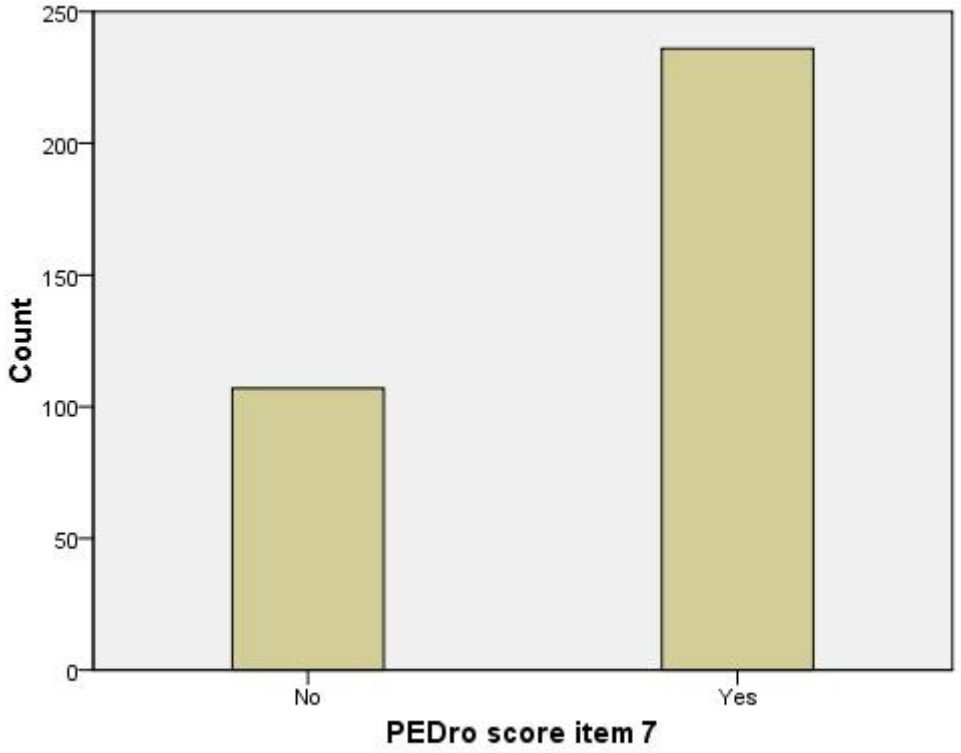
?
stroke guidelines
Canadian Stroke Network
Réseau Canadien contre les accidents cérébrovasculaires
CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada
Vancouver Coastal Health Research Institute
Healthier lives through discovery
Royal College of Physicians
SIGN
Scottish Intercollegiate Guidelines Network
American Heart Association
Learn and Live
The Stroke Association
Caring for today
Researching for tomorrow
Working for change
Agency for Science, Technology and Research
SINGAPORE
National Stroke Association
www.stroke.org
NSA
National Stroke Association
strokefoundation
KNGF
Nederlandse Vereniging voor Ergotherapie

PEDro item 3 (allocation)



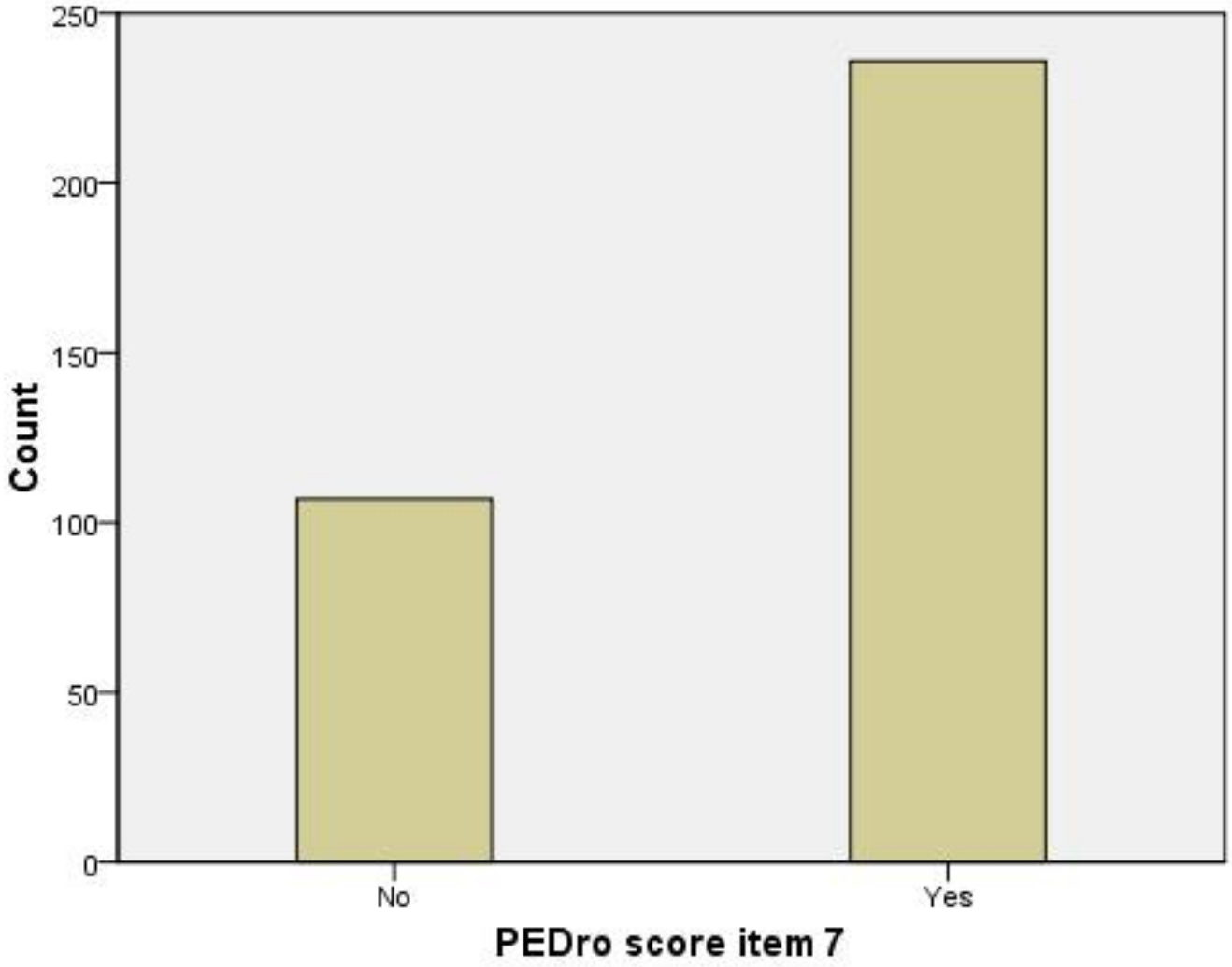
PEDro 2004-2011

PEDro item 7 (blinding)

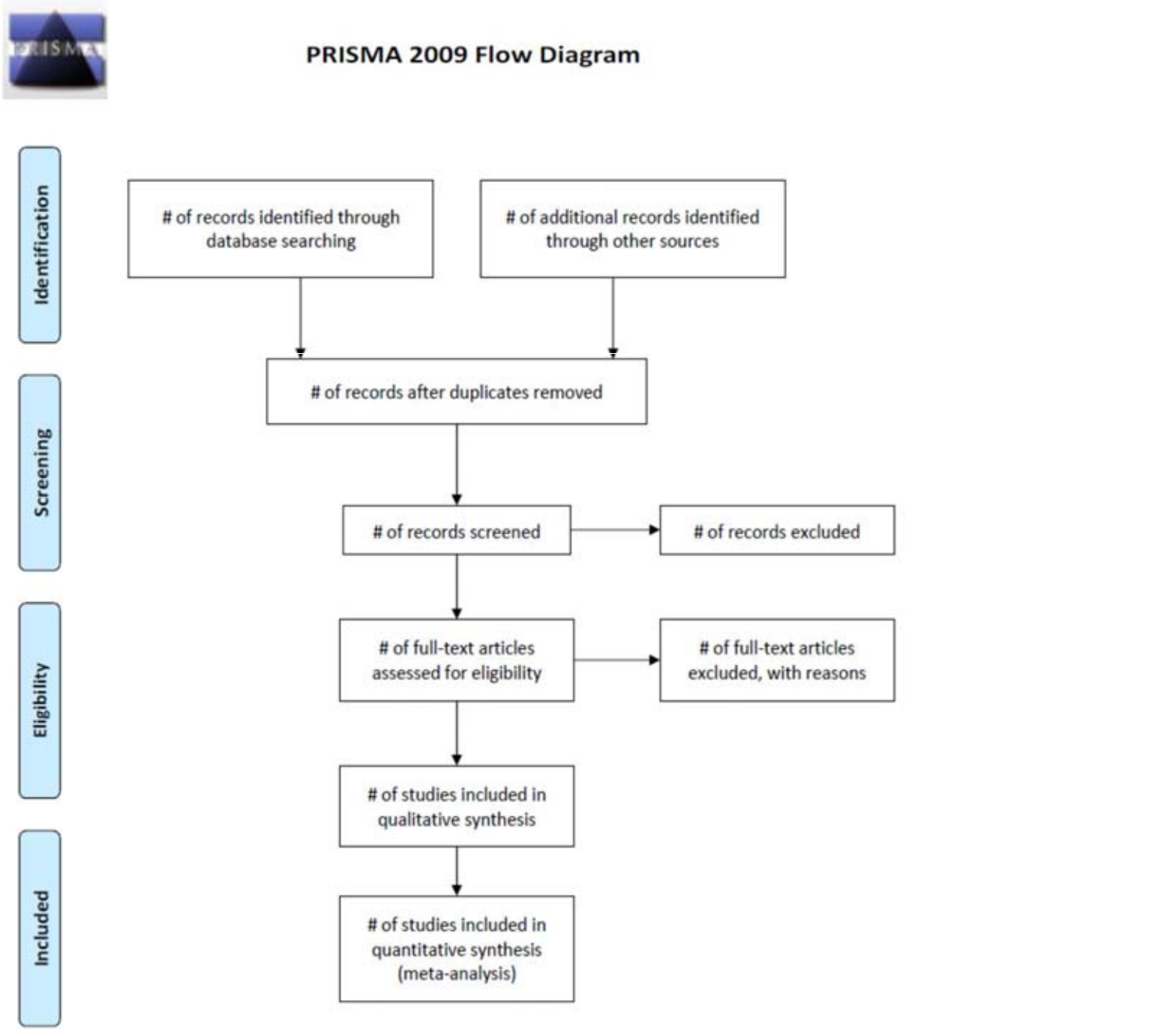


PEDro 2004-2011

PEDro item 9 (intention-to-treat)

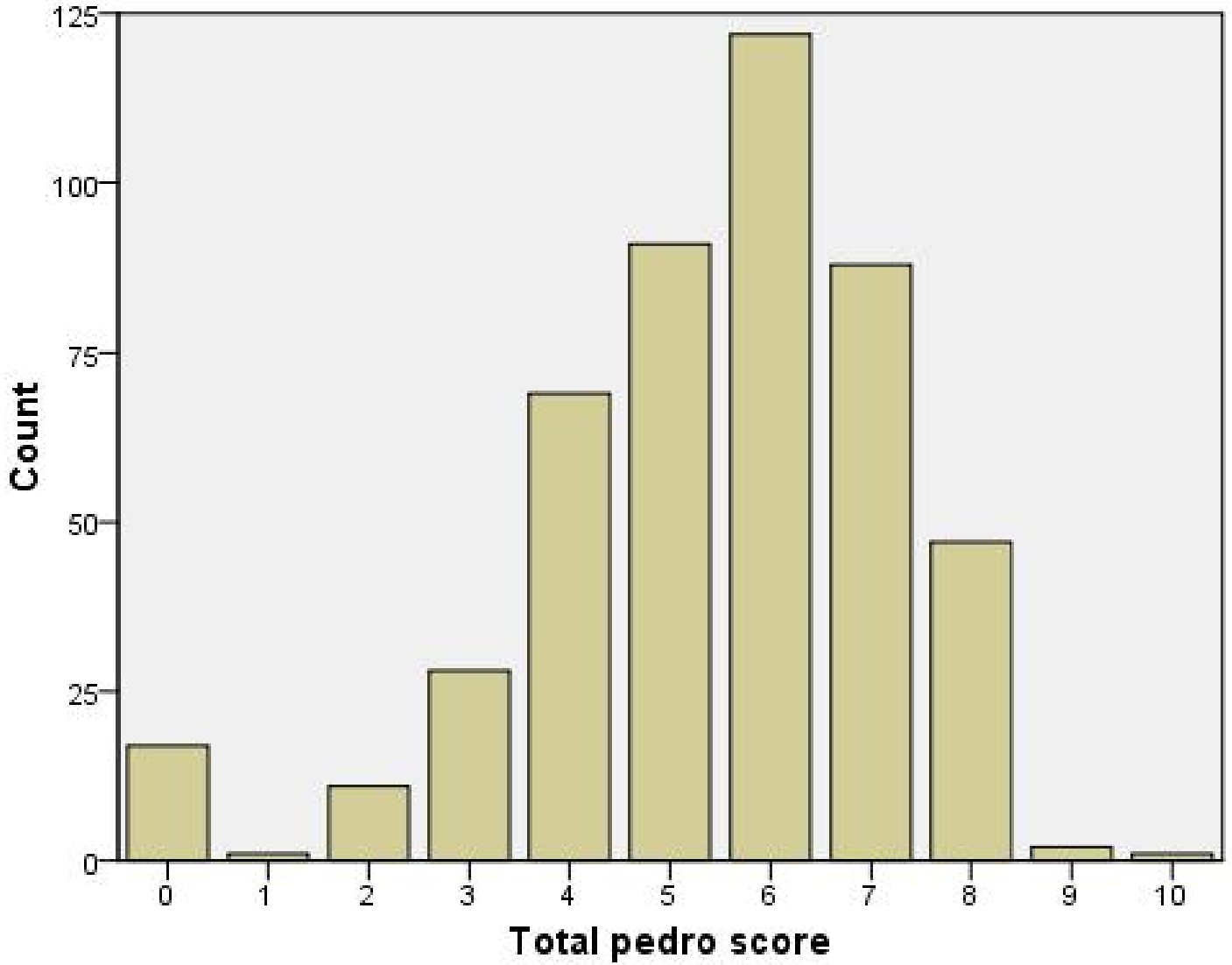


PEDro 2004-2011



http://www.prisma-statement.org/statement.htm

PEDro scores overall (n=460)



PEDro scores:

- PEDro score <2004 (N=153):
  - Mean (SD): 5.05 (1.46)
  - Median (IQR): 5 (4-6)

- PEDro score 2004-2011 (N=307 trials):
  - Mean (SD): 5.83 (1.50)
  - Median (IQR): 6 (5-7)

ELSEVIER

Journal of Clinical Epidemiology 64 (2011) 383–394

Journal of Clinical Epidemiology

GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables

Gordon Guyatt[a,b,*], Andrew D. Oxman[c], Elie A. Akl[m], Regina Kunz[d], Gunn Vist[c], Jan Brozek[a], Susan Norris[e], Yngve Falck-Ytter[f], Paul Glasziou[g], Hans deBeer[h], Roman Jaeschke[b], David Rind[i], Joerg Meerpohl[j,k], Philipp Dahm[l], Holger J. Schünemann[a,b]

Grading of Recommendations Assessment, Development, and Evaluation

In the GRADE approach, randomized controlled trials (RCTs) start as high-quality evidence and observational studies as low-quality evidence supporting estimates of intervention effects.

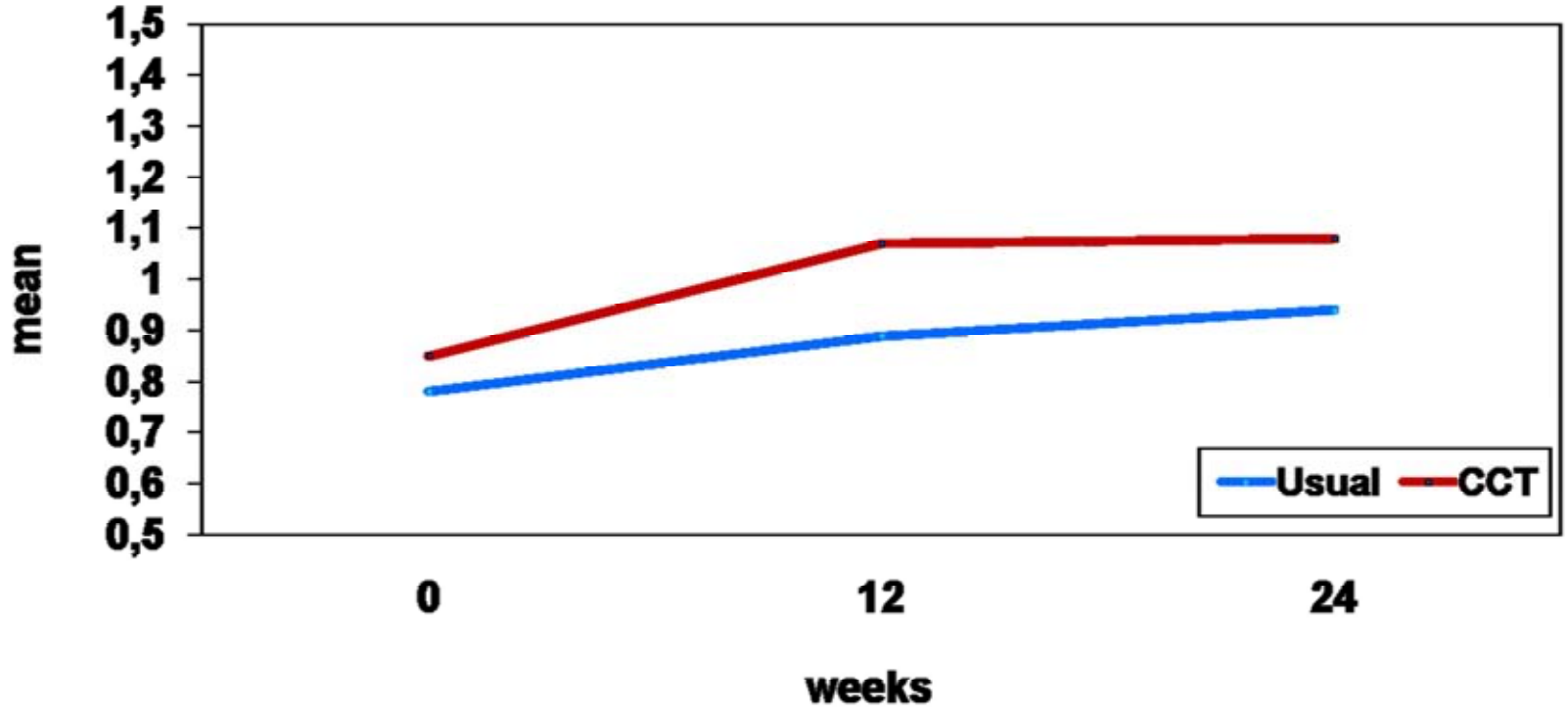
Systematic reviews and meta-analyses

- The aim of the PRISMA (**P**referred **R**eporting **I**tems for **S**ystematic **R**eviews and **M**eta-**A**nalyses) statement is to help authors report a wide array of systematic reviews to assess the benefits and harms of a health care intervention.

- PRISMA focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses by a checklist of 27 items.

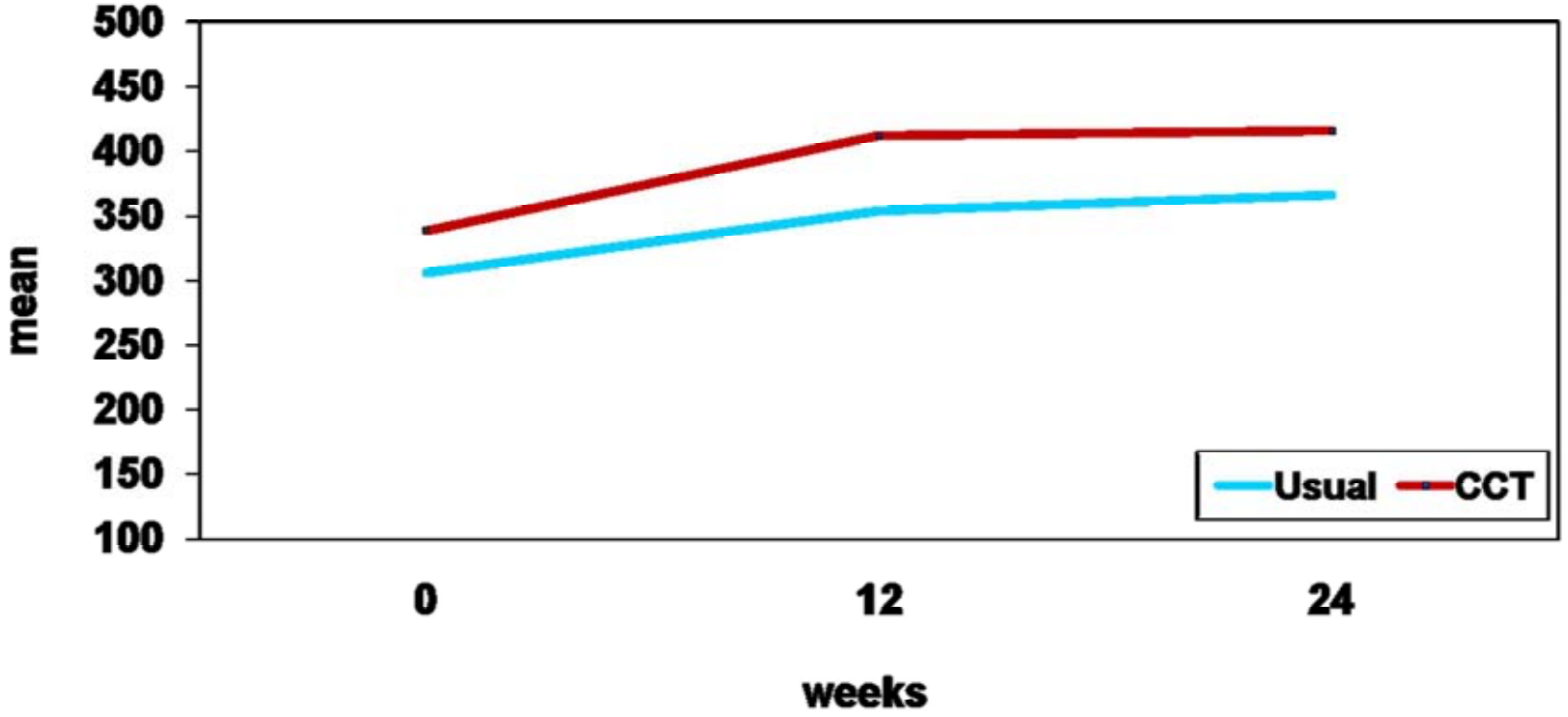
http://www.prisma-statement.org/statement.htm

5 meter walking speed (N=250)



•Overall group*time effect:	?Ŧ 0.026 (0.012);	p=0.015	
•Overall time effect:	?ê 0.090 (0.009);	p<0.001	
•Intervention phase alone:	**?¨=0.091 (0.023);**	**p<0.001**	**+ 9 cm/s**
•Follow-up phase alone:	?¨=0.035 (0.017);	p<0.05	

6 Minute Walking Test (N=250)



•Overall group*time effect:	?s= 6.118 (3.951);	p=NS	
•Overall time effect:	?é= 32.127 (2.861);	p<0.001	
•Intervention:	**?æ=20.002 (7.442);**	**p=0.004**	**+ 20m**
•Follow-up	?æ -8.274 (4.450);	p=NS	

Table I. Quality assessment of reports of prognostic studies[1-4]

OUTCOME STRATEGIES		SCALE	CRITERIA
Evaluation of			
Study design			
D1	Source population and recruitment	Y/N/?	Positive when sampling frame (e.g. hospital-based, community-based, primary care) and recruitment procedure (place and time-period, method used to identify sample) are reported.
D2	Inclusion and exclusion criteria	Y/?	Positive if both the inclusion and exclusion criteria are explicit described.
D3	Important baseline key characteristics of study sample	Y/?	Positive if the following key characteristics of the sample are described: gender, age, type, localization, number of strokes*, stroke severity. *Number of strokes is adequate when at least 'a history of stroke' or 'recurrent stroke' is reported.
D4	Prospective design	Y/N/?	Positive when a prospective design was used, or in case of a historical cohort in which prognostic factors are measured before the outcome is determined.
D5	Inception cohort	Y/N/?	Positive if observation started at a uniform time point within two weeks after stroke onset.
D6	Information about treatment	Y/N/?	Positive if information on treatment during observation period is reported (e.g. (para)medical, usual care, randomized, etc.).
Study attrition			
A1	Number of loss to follow-up	Y/N/?	Positive if number of loss to follow-up during period of observation did not exceed 20%.
A2	Reasons for loss to follow-up	Y/N/?	Positive if reasons for loss to follow-up are specified, or there was no loss to follow-up.
A3	Methods dealing with missing data	Y/N/?	Positive, if in case of missing values the method of dealing with missing values is adequate (e.g. multiple imputation), or there are no missing values.
A4	Comparison completers and non-completers	Y/N/?	Positive if article mentions that there are no significant differences between participants who completed the study and who did not, concerning key characteristics gender, age, type and severity and candidate predictors and outcome, or there was no loss to follow-up.
Predictor measurement			
P1	Definition of predictors	Y/?	Positive if the article clearly defines or describes all candidate predictors (concerning *both* clinical and demographic features).
P2	Measurement of predictors reliable and valid	Y/N/?	Positive if ≥1 candidate predictors are measured in a valid and reliable way, or referral is made to other studies which have established reliability and validity.
P3	Coding scheme and cut-off points	Y/N/?	Positive if coding scheme for candidate predictors were defined, including cut-off points and rationale for cut-off points was given; or if there was no dichotomization or classification.
P4	Data presentation	Y/N/?	Positive if frequencies or percentages or mean (SD/CI), or median (IQR) are reported of all candidate predictors.

Outcome measurement			
O1	Outcome(s) defined	Y/N/?	Positive when a clear definition of the outcome(s) of interest is presented.
O2	Measurement of outcome(s) reliable and valid	Y/N/?	Positive when outcome is measured in a valid and reliable way, or there is referred to other studies which have established reliability and validity.
O3	Coding scheme and cut-off points described	Y/N/?	Positive if coding scheme of the outcome was defined, including cut-off points and rationale for cut-off points was given; or if there was no dichotomization.
O4	Appropriate end-points of observation	Y/N/?	Positive if observation was obtained at a fixed moment after stroke onset, negative when observation was obtained at discharge.
O5	Data presentation	Y/N/?	Positive if frequencies or percentages or mean (SD/CI) or median (IQR) are reported of the outcome measure.
Statistical analysis			
S1	Strategy for model building described	Y/N/?	Positive if the method of the selection process for multivariable analysis is presented (e.g. forward, backward selection, including p-value).
S2	Sufficient sample size	Y/N/?	Positive if in logistic regression analysis number of patients with a positive or negative outcome (event) per variable is adequate, i.e. is equal to or exceeds 10 events per variable in the multivariable model (EPV), or in case of linear regression analysis, N is ≥100.
S3	Presentation univariable analysis	Y/N/?	Positive if univariable crude estimates and confidence intervals (β/SE, OR/CI, RR, HR) are reported. Negative when only p-values or correlation coefficients are given, or if no tests are performed at all.
S4	Presentation multivariable analysis	Y/N/?	Positive if for the multivariable models point estimates with confidence intervals (β/SE, OR/CI, RR, HR,) are reported.
S5	Continuous predictors	Y/N/?	Positive if continuous predictors are not dichotomized in the multivariable model.
Clinical performance/validity			
C1	Clinical performance	Y/?	Positive if article provides information concerning ≥1 of the following performance measures: discrimination (e.g. ROC), calibration (e.g. HL statistic), explained variance, clinical usefulness (e.g. sensitivity, specificity, PPV, NPV)
C2	Internal validation	Y/?	Positive if appropriate techniques are used to assess internal validity (e.g. cross-validation, bootstrapping), negative if split-sample method was used.
C3	External validation	Y/?	Positive if the prediction model was validated in a second independent group of stroke patients.

Y, Positive, 1 point; N, Negative, 0 points; ?, Partial/unknown

1. Hayden J, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2004;144:427-437.
2. Counsell C, Dennis M. Systematic review of prognostic models in patients with acute stroke. Cerebrovasc Dis. 2001;12:159-170.
3. Kwakkel G, Wagenaar R, Kollen B, Lankhorst G. Predicting disability in stroke -- A critical review of the literature. Age Ageing. 1996;25:479-489.
4. Altman D. Systematic reviews of evaluations of prognostic variables. BMJ. 2001;323:224-228.

Design FIT-STROKE trial