Sequential Parallel Comparison Design (SPCD) in CNS Clinical Trials

Maurizio Fava, MD

Executive Vice Chair, Department of Psychiatry

Director, Depression Clinical and Research Program
Massachusetts General Hospital (MGH)

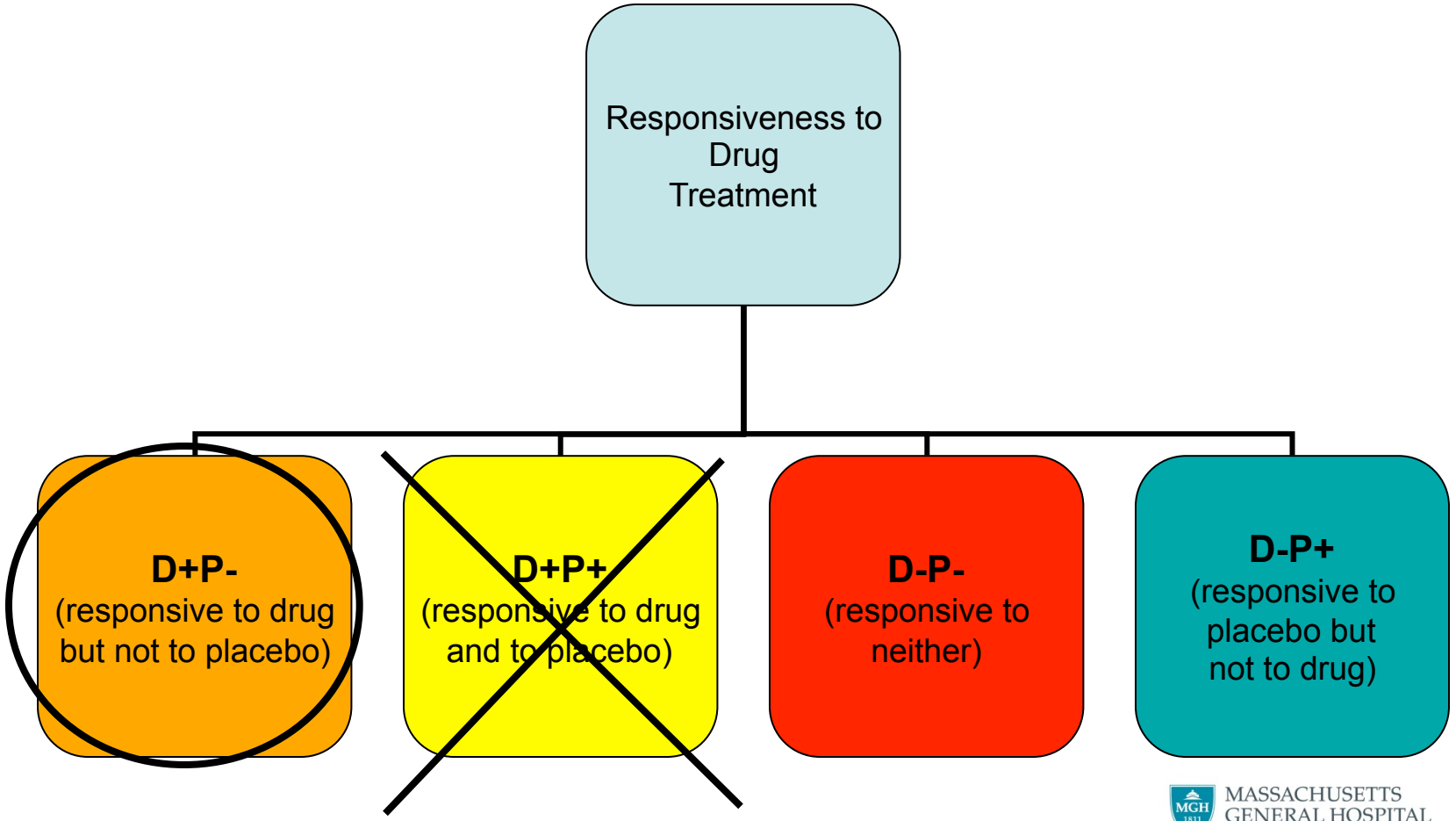
Executive Director, MGH Psychiatry CTNI
Slater Family Professor of Psychiatry
Harvard Medical School

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Disclosure (lifetime): Maurizio Fava, MD

Type	Company
Advisory Board/ Consultant	Abbott Laboratories; Affectis Pharmaceuticals AG; Alkermes, Inc.; Amarin Pharma Inc.; Aspect Medical Systems; AstraZeneca; Auspex Pharmaceuticals; Bayer AG; Best Practice Project Management, Inc.; BioMarin Pharmaceuticals, Inc.; Biovail Corporation; BrainCells Inc; Bristol-Myers Squibb; CeNeRx BioPharma; Cephalon, Inc.; CNS Response, Inc.; Compellis Pharmaceuticals; Cypress Pharmaceutical, Inc.; DiagnoSearch Life Sciences (P) Ltd.; Dinippon Sumitomo Pharma Co. Inc.; Dov Pharmaceuticals, Inc.; Edgemont Pharmaceuticals, Inc.; Eisai Inc.; Eli Lilly and Company; ePharmaSolutions; EPIX Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Fabre-Kramer Pharmaceuticals, Inc.; Forest Pharmaceuticals, Inc.; GenOmind, LLC; GlaxoSmithKline; Grunenthal GmbH; i3 Innovus/Ingenis; Janssen Pharmaceutica; Jazz Pharmaceuticals, Inc.; Johnson & Johnson Pharmaceutical Research & Development, LLC; Knoll Pharmaceuticals Corp.; Labopharm Inc.; Lorex Pharmaceuticals; Lundbeck Inc.; MedAvante, Inc.; Merck & Co., Inc.; MSI Methylation Sciences, Inc.; Naurex, Inc.; Neuralstem, Inc.;Neuronetics, Inc.; NextWave Pharmaceuticals; Novartis AG; Nutrition 21; Orexigen Therapeutics, Inc.; Organon Pharmaceuticals; Otsuka Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; PharmaStar; Pharmavite® LLC.; PharmoRx Therapeutics; Precision Human Biolaboratory; Prexa Pharmaceuticals, Inc.; Puretech Ventures; PsychoGenics; Psylin Neurosciences, Inc.; Rexahn Pharmaceuticals, Inc.; Ridge Diagnostics, Inc.; Roche; Sanofi-Aventis US LLC.; Sepracor Inc.; Servier Laboratories; Schering-Plough Corporation; Solvay Pharmaceuticals, Inc.; Somaxon Pharmaceuticals, Inc.; Somerset Pharmaceuticals, Inc.; Sunovion Pharmaceuticals; Supernus Pharmaceuticals, Inc.;Synthelabo; Takeda Pharmaceutical Company Limited; Tal Medical, Inc.; Tetragenex Pharmaceuticals, Inc.; TransForm Pharmaceuticals, Inc.; Transcept Pharmaceuticals, Inc.; Vanda Pharmaceuticals, Inc.
Speaking/ Publishing	Adamed, Co; Advanced Meeting Partners; American Psychiatric Association; American Society of Clinical Psychopharmacology; AstraZeneca; Belvoir Media Group; Boehringer Ingelheim GmbH; Bristol-Myers Squibb; Cephalon, Inc.; CME Institute/Physicians Postgraduate Press, Inc.; Eli Lilly and Company; Forest Pharmaceuticals, Inc.; GlaxoSmithKline; Imedex, LLC; MGH Psychiatry Academy/Primedia; MGH Psychiatry Academy/Reed Elsevier; Novartis AG; Organon Pharmaceuticals; Pfizer Inc.; PharmaStar; United BioSource,Corp.; Wyeth-Ayerst Laboratories
Research Support	Abbott Laboratories; Alkermes, Inc.; Aspect Medical Systems; AstraZeneca; BioResearch; BrainCells Inc.; Bristol-Myers Squibb; Cephalon, Inc.; CeNeRx BioPharma; Clintara, LLC; Covidien; Eli Lilly and Company; EnVivo Pharmaceuticals, Inc.; Euthymics Bioscience, Inc.; Forest Pharmaceuticals, Inc.; Ganeden Biotech, Inc.; GlaxoSmithKline; Icon Clinical Research; i3 Innovus/Ingenix; Johnson & Johnson Pharmaceutical Research & Development; Lichtwer Pharma GmbH; Lorex Pharmaceuticals; NARSAD; NCCAM; NIDA; NIMH; Novartis AG; Organon Pharmaceuticals; PamLab, LLC.; Pfizer Inc.; Pharmavite® LLC; Photothera; Roche; RCT Logic, LLC (formerly Clinical Trials Solutions, LLC) ; Sanofi-Aventis US LLC; Shire; Solvay Pharmaceuticals, Inc.; Synthelabo; Wyeth-Ayerst Laboratories
Stock/Other Financial Options	Compellis Pharmaceuticals Patents for Sequential Parallel Comparison Design (SPCD), which are licensed by MGH to RCT Logic, LLC; patent application for a combination of azapirones and bupropion in Major Depressive Disorder (MDD); for research and licensing of SPCD with RCT Logic. Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), and SAFER; Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing Co. Pte.Ltd.

Subpopulations of Patients Based on their Responsiveness to Treatment



MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

What are the Inclusion and Exclusion Criteria Issues and Possible Solutions?

- Diagnostic misclassification
  - Use of structured interviews and rater certification
  - Independent diagnostic interviews or verifications of inclusion criteria
- Transient or atypical forms of illness
  - SAFER Criteria Interview
- Bias to enroll at all costs – grade inflation
  - Interactive Voice Response (IVR) methods
  - Remote, independent interviews

Fava M et al; Psychother Psychosom. 2003 May-Jun;72(3):115-27

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

What are the Inclusion and Exclusion Criteria Issues and Possible Solutions?

- Diagnostic misclassification
  - Use of structured interviews and rater certification
  - Independent diagnostic interviews or verifications of inclusion criteria
- Transient or atypical forms of illness
  - SAFER Criteria Interview
- Bias to enroll at all costs – grade inflation
  - Interactive Voice Response (IVR) methods
  - Remote, independent interviews

Fava M et al; Psychother Psychosom. 2003 May-Jun;72(3):115-27

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Requirements for a Valid Patient/ Illness: The SAFER Criteria

- State vs Trait: the identified symptoms must reflect the current *state* of illness and not long-standing traits
  - Traits do not generally change in 4-12 weeks
  - In the event that the patient has a lifelong illness (e.g., GAD, dysthymic disorder), there has to be clear evidence of recent, yet persistent worsening of symptoms
- Assessability: patient's symptoms are measurable with standard instruments
  - Within the context of heterogeneous clinical manifestations of the same clinical syndrome, the symptoms of valid patients *can be reliably assessed with* measurement tools
- Face validity: is the patient presentation consistent with our knowledge of the illness?
  - Are symptoms and course of illness consistent with our knowledge?
- Ecological validity: do the patient's symptoms reflect the characteristics of the illness in real-world settings?
- Rule of the Three Ps: Identified symptoms must be pervasive, persistent, pathological
  - The three Ps must interfere with function and quality of life

Targum SD, Pollack MH, Fava M. CNS Neurosci Ther. 2008 Spring;14(1):2-9.

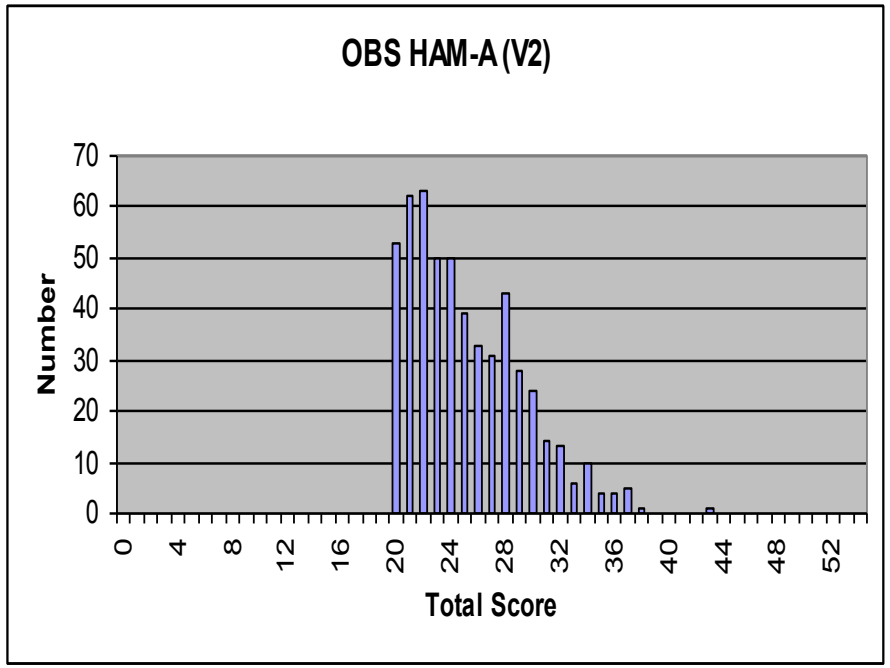
What are the Inclusion and Exclusion Criteria Issues and Possible Solutions?

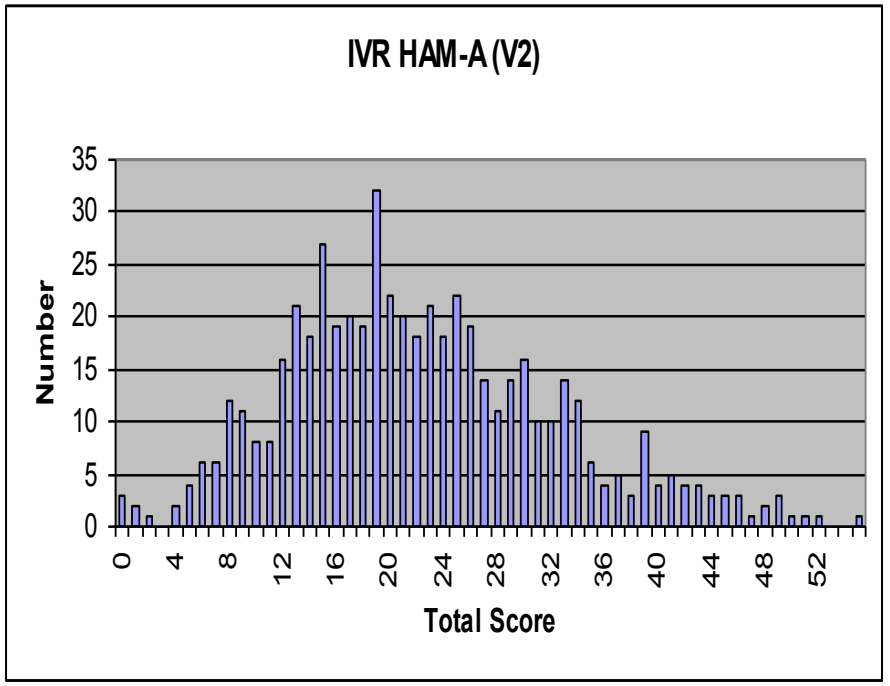
- Diagnostic misclassification
  - Use of structured interviews and rater certification
  - Independent diagnostic interviews or verifications of inclusion criteria
- Transient or atypical forms of illness
  - SAFER Criteria Interview
- Bias to enroll at all costs – grade inflation
  - Interactive Voice Response (IVR) methods
  - Remote, independent interviews

Fava M et al; Psychother Psychosom. 2003 May-Jun;72(3):115-27

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

IVR vs Clinician-Raters' Assessments of GAD Severity at Screening and Baseline





[2]Feltner, D. E., Kobak, K. A., Crockatt, J., Haber, H., Kavoussi, R., Pande, A., & Greist, J. H. (May, 2001). Interactive Voice Response (IVR) for Patient Screening of Anxiety in a Clinical Drug Trial. National Institute of Mental Health, New Clinical Drug Evaluation Unit, 41st Annual Meeting, Phoenix, AZ.

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

What are the Study Implementation Issues and Possible Solutions?

- Consent forms enhancing expectations about the trial
  - Increase chances of placebo assignment
- Lack of sensitivity of outcome measures
  - Selection of more sensitive measures
- Measurement errors/poor quality of ratings
  - Rater training, certification, and prevention of rater's drift
  - Remote, independent interviews
- Increase of non-specific, psychotherapeutic effects
  - Use of same rater

Fava M et al; Psychother Psychosom. 2003 May-Jun;72(3):115-27

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Do Expectations Affect the Degree of Placebo Response in MDD?

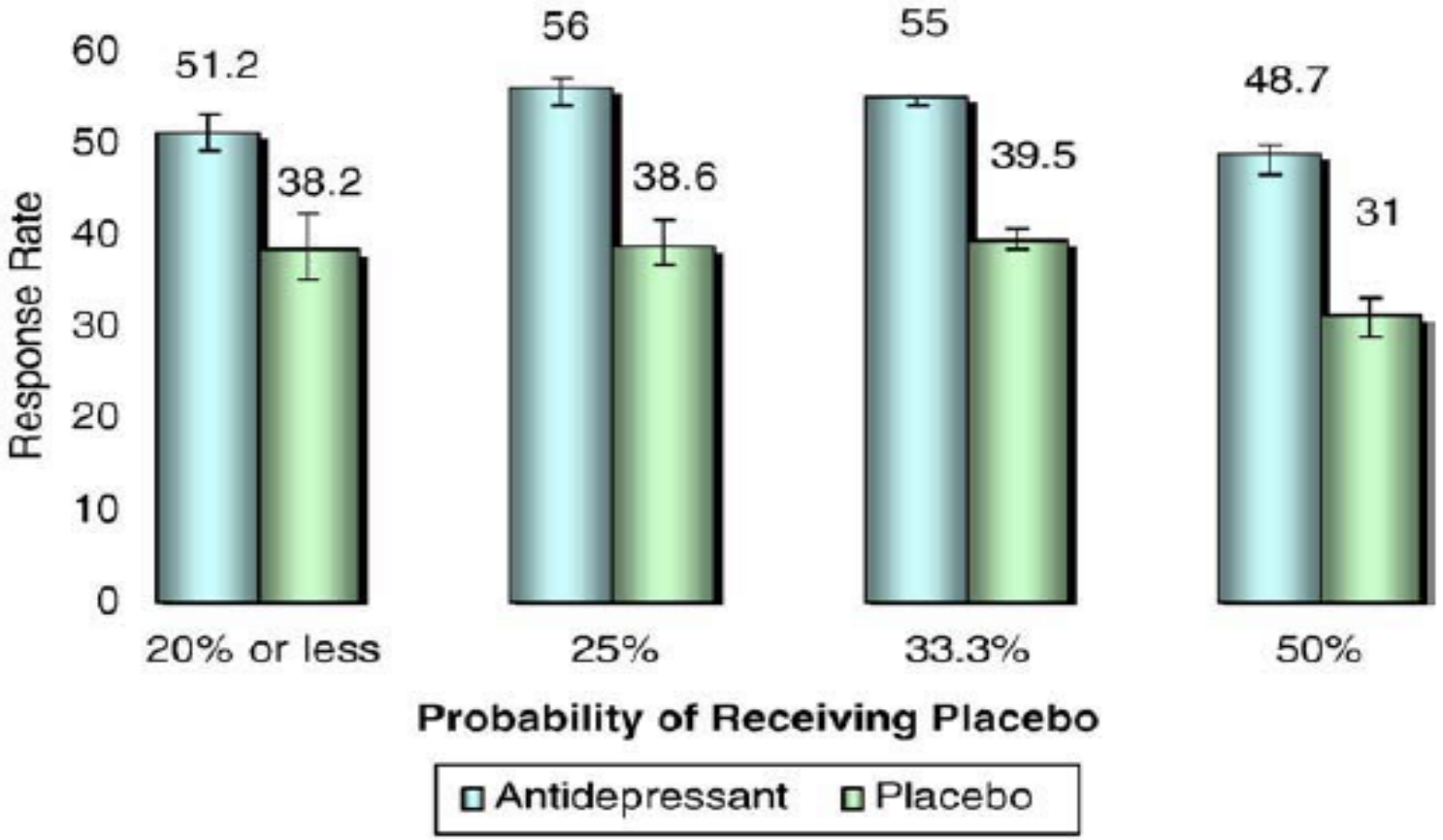


Figure 2 Probability of placebo and response rates. (N=36,385; 262 drug-placebo pair-wise comparisons).

Papakostas G and Fava M, Eur Neuropsychopharmacol. 2009 Jan;19(1):34-40.

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

What are the Study Implementation Issues and Possible Solutions?

- Consent forms enhancing expectations about the trial
  - Increase chances of placebo assignment
- Lack of sensitivity of outcome measures
  - Selection of more sensitive measures
- Measurement errors/poor quality of ratings
  - Training of study participants in the use of the self-rating measures
  - When appropriate, rater training and certification, prevention of rater's drift, independent ratings
- Increase of non-specific, psychotherapeutic effects
  - Use of same rater

Fava M et al; Psychother Psychosom. 2003 May-Jun;72(3):115-27

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Outcome Measures in Placebo-Controlled Trials of Osteoarthritis: Responsiveness to Treatment Effects in the REPORT Database

Table III

Treatment vs placebo group differences and SESs for patient- and clinician-rated outcome measures for recommended treatments

Measure	Patient global			Patient treatment response			Patient responder (% patients)			Clinician global			Clinician treatment response			Clinician responder (% patients)		
	N*	Mean	95% CI†	N	Mean	95% CI	N	Mean	95% CI	N	Mean	95% CI	N	Mean	95% CI	N	Mean	95% CI
Treatment vs placebo group difference																		
All scales, random effects model‡	26	10.7	8.5, 12.9	5	17.1	13.2, 21.0	41	23.1	19.8, 26.4	18	8.6	6.6, 10.6				28	24.5	19.6, 29.4
Scales ≥10 categories, random effects model‡	20	10.1	7.5, 12.7							7	5.6	3.4, 7.8						
Scales < 10 categories, random effects model‡	6	13.2	10.0, 16.4	5	17.1	13.2, 21.0	41	23.1	19.8, 26.4	11	10.9	8.8, 13.0				28	24.5	19.6, 29.4
All scales, unweighted, all arms§	61	12.0		20	15.5		56	23.1		48	10.9		11	18.4		34	24.5	

Dworkin et al, Osteoarthritis and Cartilage 19 (2011) 483-492

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

What are the Study Implementation Issues and Possible Solutions?

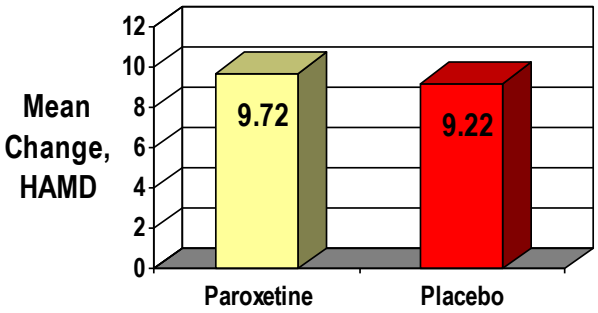
- Consent forms enhancing expectations about the trial
  - Increase chances of placebo assignment
- Lack of sensitivity of outcome measures
  - Selection of more sensitive measures
- Measurement errors/poor quality of ratings
  - Training of study participants in the use of the self-rating measures
  - When appropriate, rater training and certification, prevention of rater's drift, independent ratings
- Increase of non-specific, psychotherapeutic effects
  - Use of same rater

Fava M et al; Psychother Psychosom. 2003 May-Jun;72(3):115-27

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

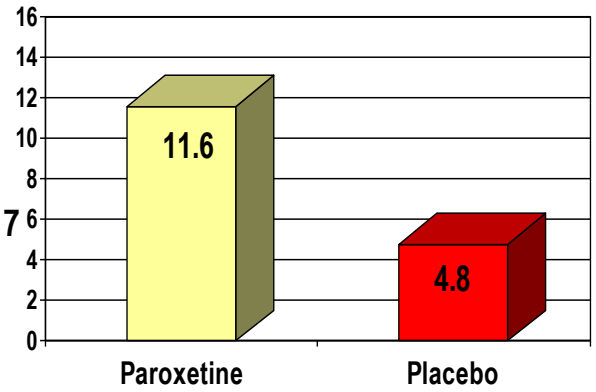
Effects of Quality of Ratings on Drug-Placebo Differences

All Subjects (Paroxetine & Placebo Arms (N=216)



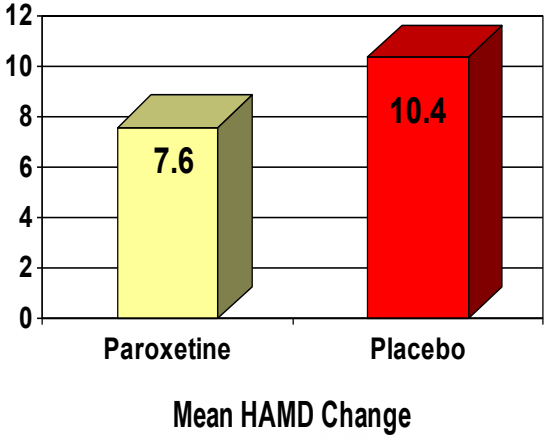
t(214)=0.505, p=.614

Good or Excellent Ratings Only



t(20)=2.612, p=.017

Fair or Poor Ratings Only

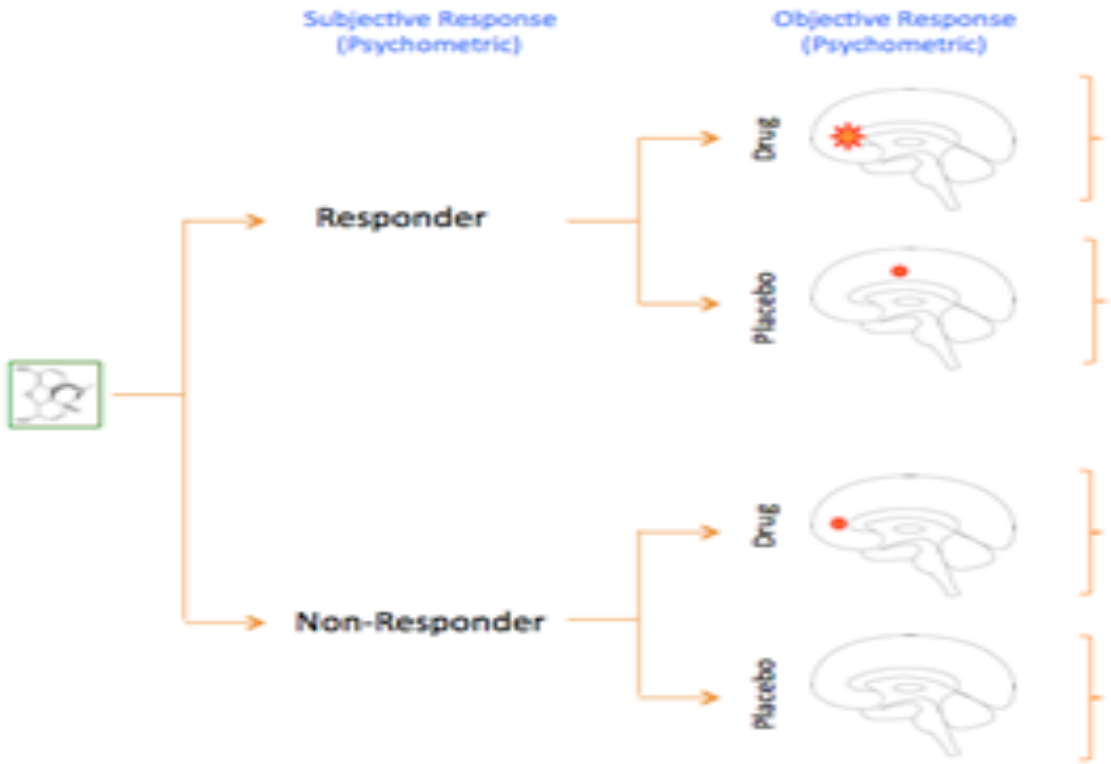


t(32)=-1.13, p=.266

Kobak, K.A., Feiger, A. D., & Lipsitz, J.D. Impact of interview quality on signal detection, *American Journal of Psychiatry*, 2005, 162, 628.

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Using Neuroimaging To Differentiate Placebo from Drug Response in Pain Trials



Borsook, Becerra, and Fava, submitted for publication

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Placebo Response in Neuropathic Pain Trials

Table 1
Responses to placebo in randomized, double-blind parallel design trials in neuropathic pain

Drug	Placebo group sample size	Endpoint week	Mean % change from baseline*	Proportion of responders (⩾50% pain reduction)	Proportion discontinuing for lack of efficacy	Ref.
Lamotrigine-30004	85	19	35%	27%	n/a	[28][a]
Lacosamide-614	59	10	34%	n/a	6.8%	[16]
Duloxetine HMAW	116	12	33%	26%	3.5%	[8][b]
Topiramate-003	126	18	32%	n/a	21%	[25]
Oxcarbazepine	70	16	31%	n/a	4.3%	[9]
Pregabalin-040	81	8	29%	30%	11.1%	[cd]
Topiramate-002	119	22	28%	n/a	24%	[28]
Lacosamide-768	64	18	27%	27%	3.1%	[e]
Oxcarbazepine	89	16	27%	n/a	5.6%	[2]
Duloxetine	116	12	27%	30%	n/a	[14]
Pregabalin-149	97	12	27%	30%	11.5%	[26][c]
Venlafaxine	81	6	27%	34%	6.3%	[21]
Lamotrigine-30005	84	19	26%	23%	n/a	[28][a]
Topiramate-001	136	22	25%	n/a	20%	[25]
Lacosamide-742	90	18	24%	24%	2.2%	[f]
Duloxetine HMAV	108	12	24%	27%	4.6%	[30][b]
Pregabalin-029	97	5	23%	18%	2.1%	[11][c]
Lacosamide-743	74	18	23%	n/a	n/a	[g]
Topiramate	109	12	22%	21%	14.6%	[15]
Gabapentin	81	8	22%	n/a	6.2%	[1]
Pregabalin-014	85	6	20%	15%	1.2%	[18][c]
Oxycodone	77	6	22%	n/a	14.3%	[7]
Pregabalin-131	70	8	11%	15%	4.3%	[19][c]
Gabapentin 9451008	189	14	n/a	24%	2.1%	[d]
PHN						
Tramadol	63	8	44%	22%	n/a	[3]
Pregabalin-81004	90	4	25%	18%	4.4%	[d]
Pregabalin-127	84	8	17%	20%	7.1%	[4][cd]
Gabapentin	111	7	16%	14%	3.6%	[17]
Pregabalin-030	88	5	15%	17%	2.3%	[cd]
Pregabalin-196	93	13	10%	8%	23.7%	[27][c]
Gabapentin	116	8	8%	n/a	2.3%	[20]
Pregabalin-045	81	8	4%	10%	8.6%	[22][c]
Mixed						
Lamotrigine-30010	109	14	33%	36%	6.3%	[24][a]
Pregabalin-155	65	12	24%	24%	29.2%	[6][c]
Gabapentin	152	8	14%	14%	3.3%	[23]

* The mean percentage change from baseline is reported if available, else the ratio of the mean change from baseline over the mean baseline score is reported as a percentage.

[a] Available at http://ctr.gsk.co.uk/Summary/lamotrigine/studylist.asp (accessed 13 May, 2008).

[b] Available at http://www.lillytrials.com/results/by-product/results_cymbalta.html (accessed 13 May, 2008).

[c] Lyrica European Public Assessment Report, 2004. Scientific discussion. Available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/lyrica/084504en6.pdf (accessed 25 Jan., 2008).

[d] Gabapentin and pregabalin trials available at http://www.clinicaltrials.org/search/ (accessed 13 May, 2008).

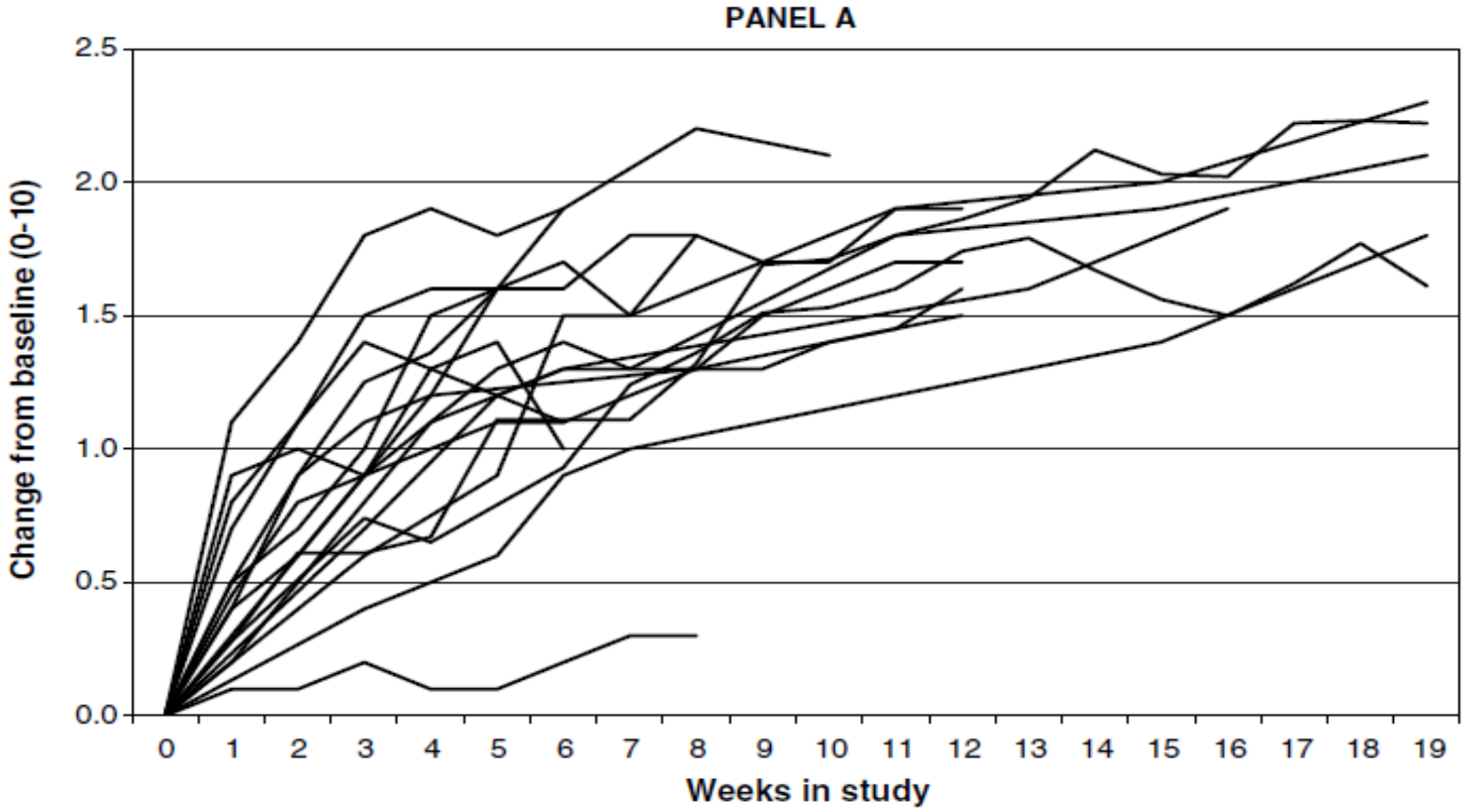
[e] Shaibani A, Kenney P, Simpson J, Bongardt S. Lacosamide in subjects with painful distal diabetic neuropathy: poster presentation Am Pain Soc, May 2006.

[f] Wymer JP, Garrison C, Simpson J, Koch B. A multicenter, randomized, double-blind, placebo-controlled trial to assess efficacy and safety of lacosamide in subjects with painful distal diabetic neuropathy: poster presentation (A202) Am Neurol Assoc 131st meeting Oct. 2006.

[g] Ziegler D, Bongardt S, Koch B, Thierfelder S. A multicenter, randomized, double-blind, placebo-controlled trial to assess efficacy and safety of lacosamide in subjects with painful distal diabetic neuropathy: poster presentation World Congress of Pain Aug. 2005.

Quessy et al, Pain 138 (2008) 479–483

Change from Baseline Pain Score (0–10) at Time Points for 17 Diabetic Neuropathic Pain Trials (VAS (0–100) Scores were Converted to a 0–10 scale)



Quessy et al, Pain 138 (2008) 479–483

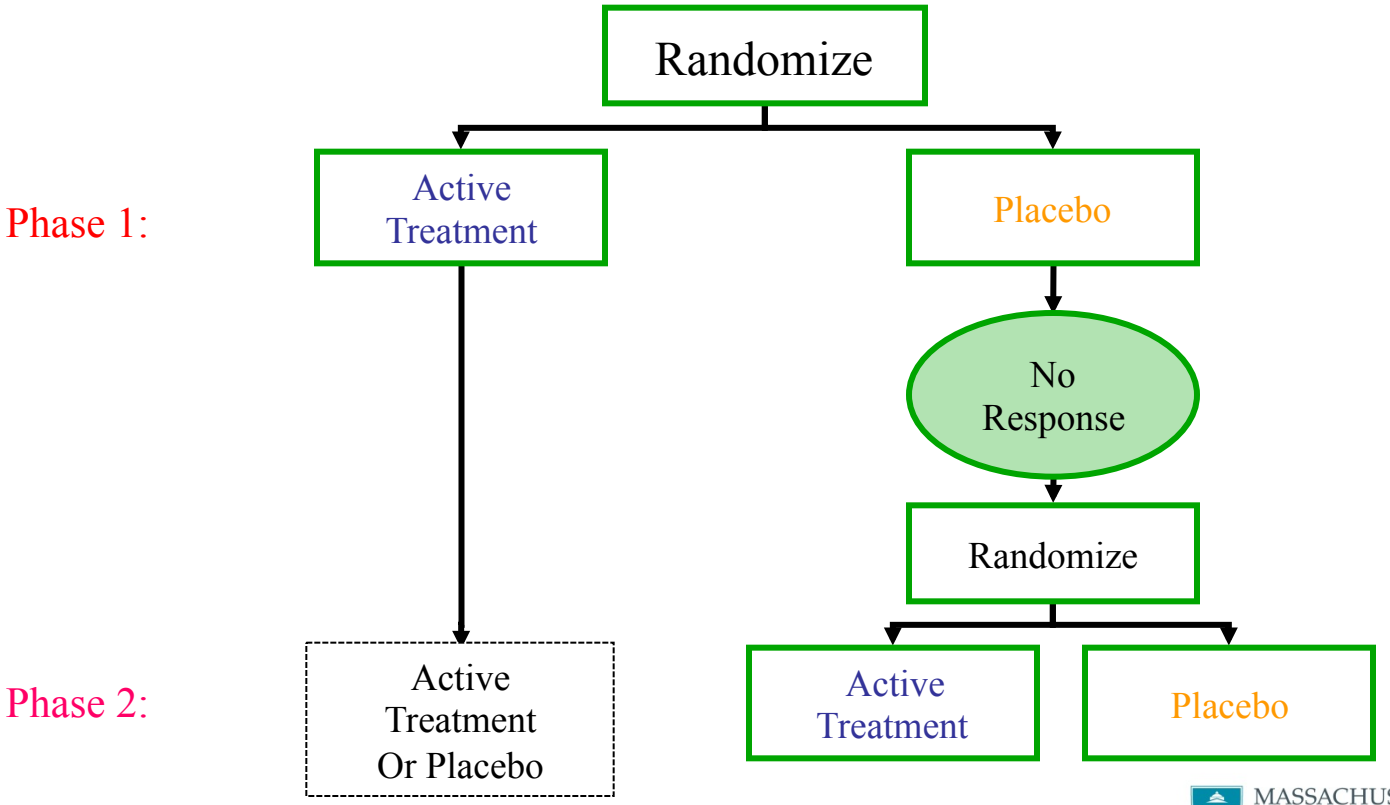
MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Sequential Parallel Comparison Design (SPCD)

- SPCD is a clinical trial methodology developed in 2003 (Fava M et al; Psychother Psychosom. 2003 May-Jun;72(3):115-27)
- SPCD is sometimes referred to as the Sequential Parallel Design (SPD)
- Format 1 of SPCD is sometimes referred to as:
  - "Sequential Parallel Design with Re-Randomization", or "SPD - ReR" (Chen et al., Contemporary Clinical Trials 32 2011; 592-604)
  - "Doubly Randomized Delayed-Start Design" (Liu et al., J Biopharm Statistics 2012; 22:4; 737-757)

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

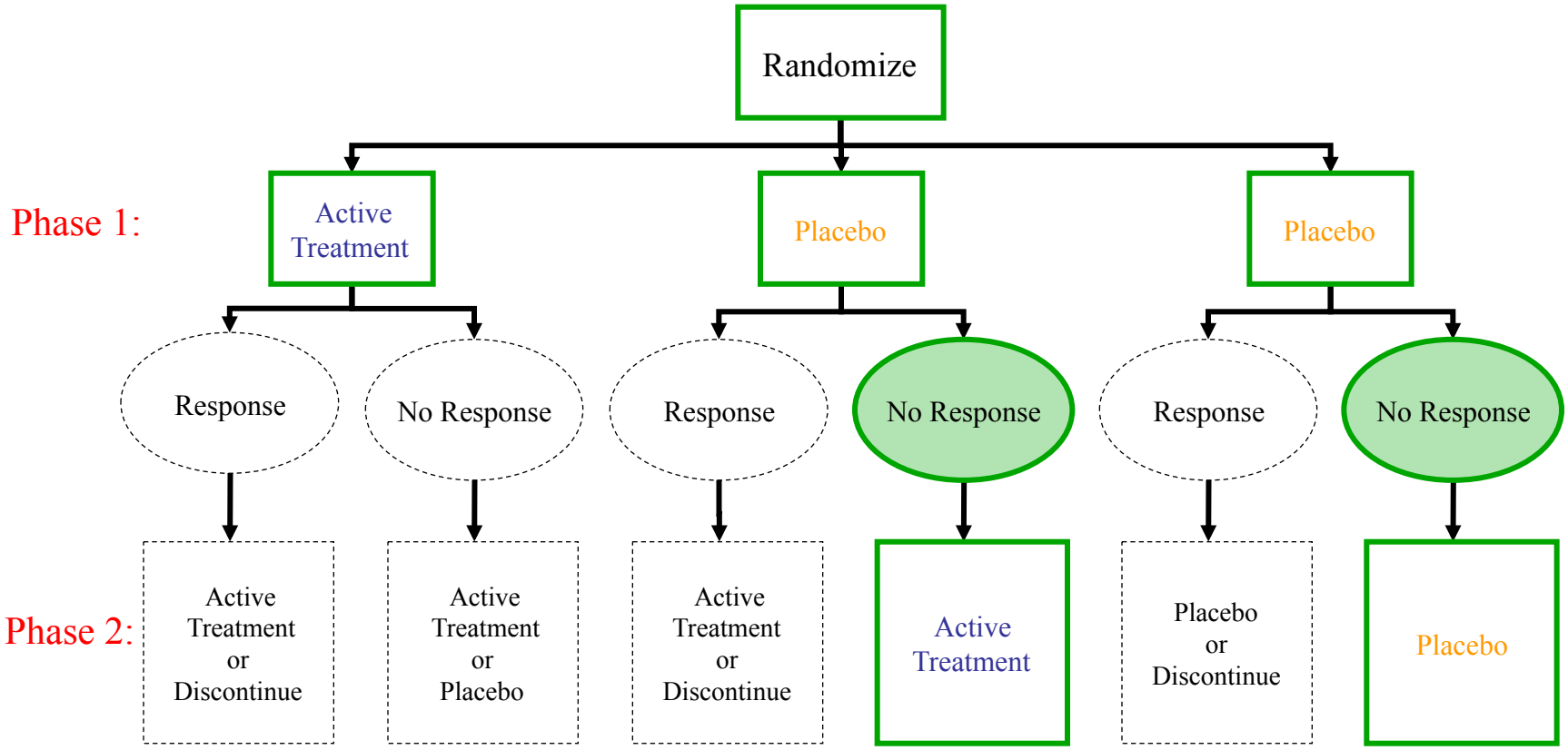
Sequential Parallel Comparison Design (SPCD) – Format 1



Fava M et al; Psychother Psychosom. 2003 May-Jun;72(3):115-27.

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Sequential Parallel Comparison Design (SPCD) – Format 2



Fava M et al; Psychother Psychosom. 2003 May-Jun;72(3):115-27.

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Why Two Phases of Treatment?

- The first phase is aimed at:
  - Comparing drug and placebo in a standard parallel comparison design fashion – drug-placebo differences are expected to be of normal size
  - Generating a large cohort of placebo non-responders
- The second phase is aimed at:
  - Comparing drug and placebo in a parallel comparison design fashion in placebo non-responders – drug-placebo differences are expected to be as large as those in the first phase or greater
  - Placebo response is expected to be smaller
- The data from the two phases are pooled to estimate the drug-placebo differences averaged (in a weighted fashion) across the two phases
- When compared to the conventional two arm clinical trial, SPCD reduces the sample size by 20–50% under a wide range of parameters, while maintaining the same power or, if the sample size remains the same, increases significantly the overall power

Fava M et al; Psychother Psychosom. 2003 May-Jun;72(3):115-27.

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

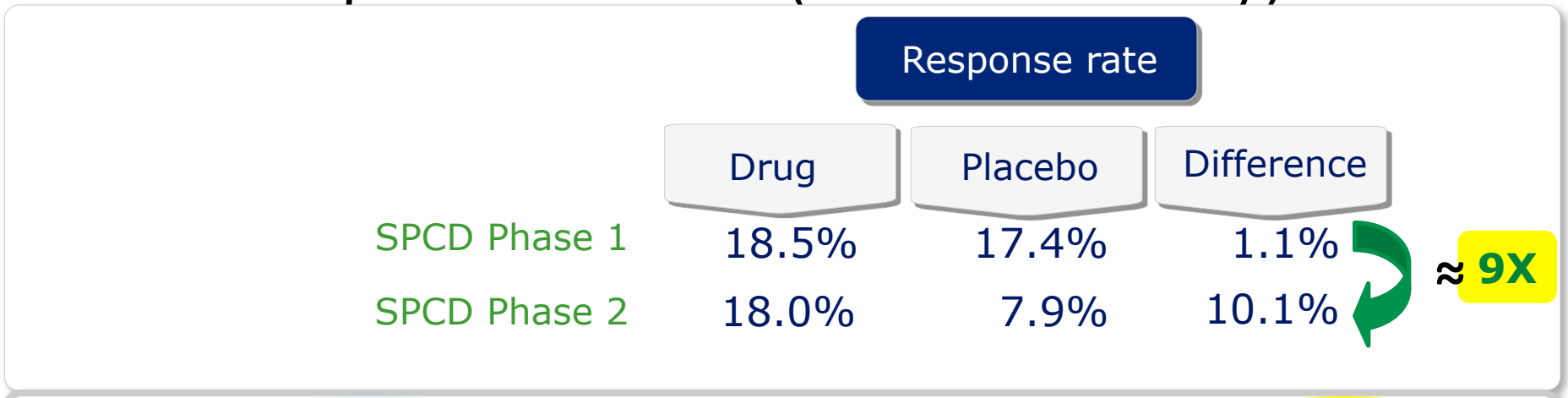
SPCD: Validity of Analytical Methods

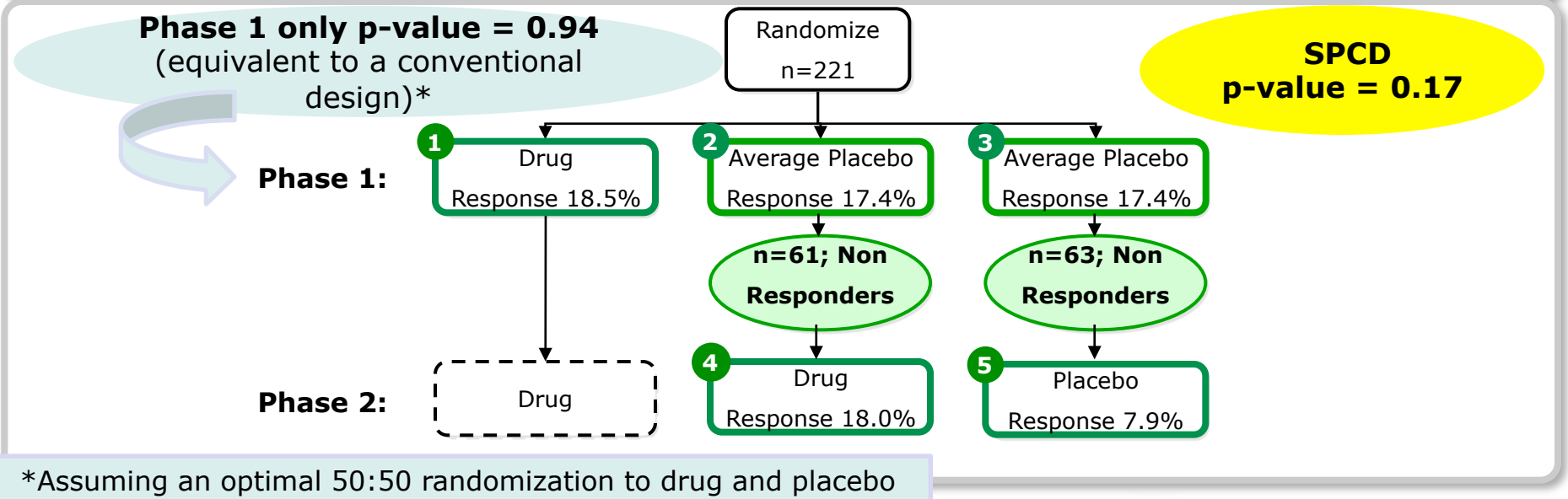
- Over the past 9 years, many biostatisticians have reviewed SPCD and have recognized that:
  - There are a number of efficient methods of aggregating the outcome data that take into account the potential correlation of observations from subjects included in more than one phase
  - There are a number of valid test statistics that preserve the type 1 error rate

SPCD: Validity of Analytical Methods

- Four Examples of Analytical Methods Proposed by Authors from Academia, Industry and FDA:
  - Categorical data
    - **Fava M., Evins A., Dorer D., Schoenfeld D.**: The Problem of the Placebo Response in Clinical Trials for Psychiatric Disorders: Culprits, Possible Remedies, and a Novel Study Design Approach; Psychotherapy and Psychosomatics 2003; 72:115-127; and Erratum 2004; 73: 123.
    - **Ivanova A., Qaqish B., Schoenfeld D.**: Optimality, sample size and power calculations for the sequential parallel comparison design; Statistics in Medicine 2011; 30: 2793-2803.
  - Continuous data
    - **Tamura R., Huang X.**: An examination of the efficiency of the sequential parallel design in psychiatric clinical trials; Clinical Trials 2007; 4:309-317.
    - **Chen Y., Yang Y., Hung H., Wang S.**: Evaluation of performance of some enrichment designs dealing with high placebo response in psychiatric clinical trials; Contemporary Clinical Trials 32 2011; 592-604.

Double-Blind Study of Low-Dose Aripiprazole Adjunctive to ADT (ADAPT-A Study)





*Assuming an optimal 50:50 randomization to drug and placebo

Fava et al, Psychother Psychosom 2012;81:87–97

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Double-Blind Study of Low-Dose Aripiprazole Adjunctive to ADT (ADAPT-A Study)

Table 4. Comparison of change of scores from baseline to the end of follow-up between treatment groups – primary efficacy sample

Measure	Drug[1] (n = 54 patients)		Placebo[1] (n = 167 patients)		Weighted difference (95% CI)	p value
	phase 1	phase 2	phase 1	phase 2		
LOCF analysis						
Baseline MADRS score	30.69 ± 4.02 (54)	26.80 ± 5.85 (61)	31.20 ± 4.75 (167)	26.29 ± 5.48 (63)	0.31 (–0.72 to 1.34)	
Follow-up MADRS score	22.15 ± 7.68 (54)	21.00 ± 8.83 (58)	23.11 ± 9.08 (167)	22.97 ± 7.79 (63)	–1.59 (–3.31 to 0.13)	
Mean change of MADRS scores from baseline	–8.54 ± 7.21 (54)	–5.80 ± 7.08 (61)	–8.09 ± 8.13 (167)	–3.32 ± 5.97 (63)	–1.51 (–3.11 to 0.09)	0.0649

Fava et al, Psychother Psychosom 2012;81:87–97

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

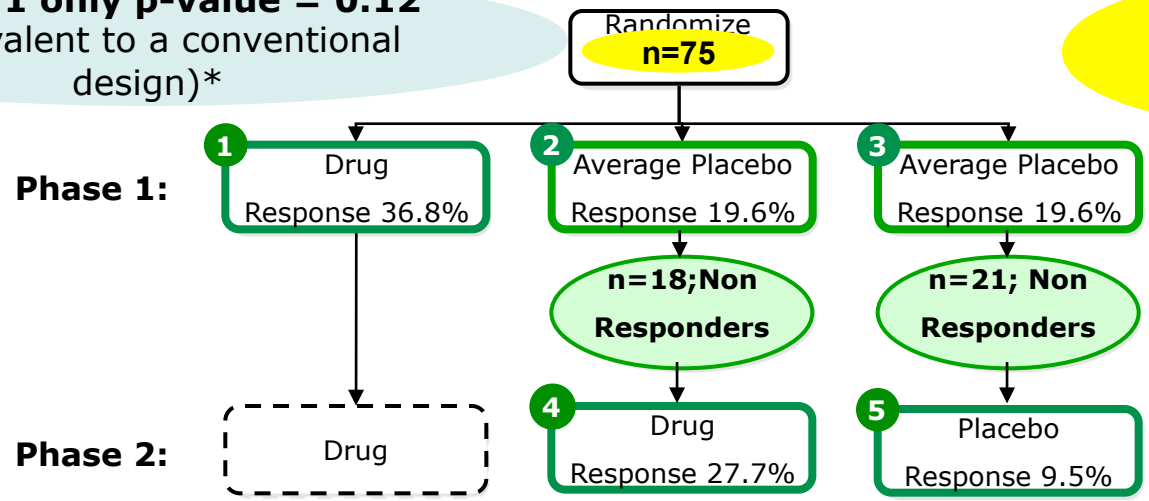
Double-Blind Study of L-Methylfolate (L-MTHF) Augmentation of SSRIs (TRD-2 Study)

Response rate	Drug	Placebo	Difference
SPCD Phase 1	36.8%	19.6%	17.2%
SPCD Phase 2	27.7%	9.5%	18.2%

≈ 1X

Phase 1 only p-value = 0.12
(equivalent to a conventional design)*

SPCD
p-value < 0.05



*Assuming an optimal 50:50 randomization to drug and placebo

Papakostas G et al, AmJ Psych, in press

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Standard Parallel Comparison Design Effects on Placebo Response

Patient Responds to:		
Placebo – Drug +	Placebo - Drug -	Placebo + Drug +
Informative	Not Informative	Not Informative
20%	**50%**	**30%**

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

SPCD Effects on Placebo Response

Patient Responds to:		
Placebo – Drug +	Placebo - Drug -	Placebo + Drug +
Application of Placebo Response Reduction Strategies		
Informative	Not Informative	Not Informative
~~**20%**~~ **31%**	**50%**	~~**30%**~~ **19%**

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Example: Extent of benefit depends upon response rates

	Response rate		
	Drug	Placebo	Difference
Single Phase Design or SPCD Phase 1	50%	30%	20%
SPCD Phase 2	30%	10%	20%

	Total *n*	
Power	Single Phase Design	SPCD
70%	148	**93**
80%	186	**119**
90%	248	**159**

	Power	
Total *n*	Single Phase Design	SPCD
100	53%	**73%**
150	71%	**89%**
200	82%	**95%**

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

SPCD - In the preceding table

- Power calculated with a calculator (developed by Drs. Ivanova and Schoenfeld) for a Sequential Parallel Comparison Design (software available at www.rctlogic.com). This software addresses either binary outcomes or continuous outcomes to analyze power and sample size for SPCD trials in comparison to trials with a conventional single phase design.
- Sample sizes and power for the single phase design and SPCD are computed based on the asymptotic formulae for corresponding two-sided score tests with (a) type I error rate of 0.05 (two-sided), (b) design parameter r=1, and (c) assumed retention of placebo non-responders from Phase 1 to Phase 2 = 90%.
- The parallel design is assumed to have active treatment and placebo groups of equal size. SPCD is assumed, in Phase 1, to have an allocation between active treatment and placebo according to a 43:57 ratio.

SPCD is a Flexible Design

- Examples of Clinical Trials Using SPCD:
  - Drug *versus* Placebo
  - Drug 1 *versus* Drug 2 *versus* Placebo*
  - Drug 1 + Drug 2 *versus* Drug 1 + Placebo**

---

*Drug 2 is an "active comparator"
**Drug 2 is "adjunct therapy"

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

SPCD Utilization

- 5 trials completed by year-end 2012 (See NCT00683852; NCT00555997; NCT00955955; and NCT00321152)
  - The enrollment of the first pivotal trial in depression trial has just been completed by pharma (NCT01318434)
- 8 new trials have started or are expected to start in 2013
  - A Phase II trial sponsored by pharma is ongoing
  - The first SPCD trial of a medical device, funded by NIH as part of the RAPID program, is expected to commence in Q4 of 2012
  - Three Phase II trials sponsored by pharma are slated to begin in Q1 of 2013
  - An NIH funded depression trial is ongoing
    - PIs at Yale, Baylor, and MGH

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Summary

- The placebo response is a major issue in CNS clinical trials
- A number of contributing factors are likely to play a key role
- Attempts to minimize the placebo response have typically led to modest results
- A cost-effective design (SPCD) that enhances signal detection has been proposed and has been or is being implemented in numerous CNS trials

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE

Summary (cont.)

- SPCD can provide greater assay sensitivity. Therefore:
  a) for any given "*n*", greater power can result, or
  b) for any given power, a smaller "*n*" can be used
- SPCD can (and has, in completed trials) significantly reduce the p-value achieved
- SPCD can provide a lower p-value by reducing the detrimental impact of placebo re

MASSACHUSETTS GENERAL HOSPITAL
CLINICAL TRIALS NETWORK AND INSTITUTE