Defining A Clinically Meaningful Effect for the Design and Interpretation of RCTs

Co-chairs:
Richard Keefe
Duke University Medical Center and NeuroCog Trials
Andy Leon
Weill Cornell Medical Center

Financial Disclosures

Past 3 Years

Consultant/Ad Board/Service Provider for: Abbott, Amgen, Astellas, Asubio, BiolineRx, Bristol-Myers-Squbb, Eli Lilly, EnVivo, Helicon, Lundbeck, Merck, Mitsubishi, Otsuka, Pfizer, Roche, Shire, Sunovion, Takeda, Targacept, WWCT

Research Funding: GSK, Allon, NIMH, Novartis, Psychogenics, Singapore Medical Research Council, Columbia University Foundation for Mental Hygiene

Founder of NeuroCog Trials, Inc., which provides rater training, data quality assurance and consultation to several pharmaceutical companies and other consortia

Royalties: Brief Assessment of Cognition in Schizophrenia (BACS), MATRICS Consensus Cognitive Battery (MCCB), Virtual Reality Functional Capacity Assessment Tool (VRFCAT)

Goals of Clinical Trials

1. Is this drug safe?
2. Is it efficacious?

.

.

.

N. Will this drug produce a clinically meaningful effect?

Beyond Efficacy in Isolation

- "Suppose a well-done randomized clinical trial (RCT) reports a statistically significant difference between treatment (T) and control (C) groups, with p=.05, p=.01, even p=10^{-6}. Should these results be automatically considered of clinical significance, the basis of recommending that clinicians use T rather than C for patients like those studied? No. What would be needed in addition to infer clinical significance is the subject of this ~~review~~ (panel)."

* Kraemer HC, Kupfer DJ. Size of Treatment Effects and Their Importance to Clinical Research and Practice. *Biol Psychiatry* 2006;59:990–996

Effect Size for a Comparison of Group Means (t-test)

$$d = \frac{\bar{X}_1 - \bar{X}_2}{s}$$

- s = pooled standard deviation for entire sample
- Ratio of between groups difference / within group differences
- Group difference in standard deviation units
- Used for CRT sample size estimates

Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York, Academic Press, 1977.

Number Needed to Treat (NNT)

$$NNT = 1/(R_A - R_C)$$

Where:

- R_A=% responders in Active group
- R_c=% responders in Control group

Examples:

- NNT=1/(50% – 40%) = 10
- NNT=1/(50% – 10%) = 2.5

NNTs and ESs*

Table 1. Cohen's *d* and Its Rescaling *r* for Outcome Data Having Normal Distributions with Equal Variances in the Treatment and Control Groups, Translated to the Equivalent Values of AUC, SRD, and NNT

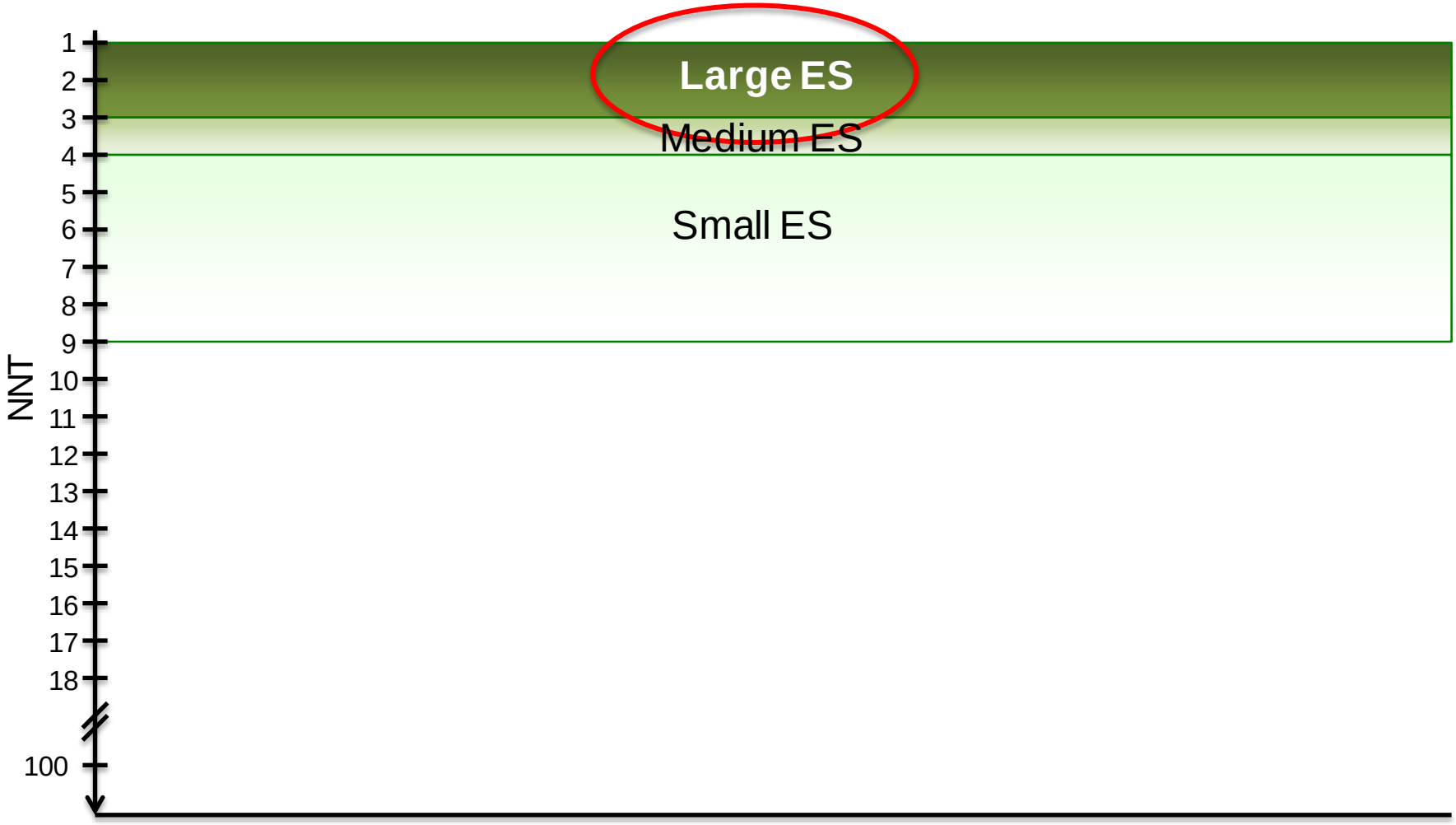
Cohen's *d*	*r*	AUC	SRD	NNT	*n* for 80% Power
−∞	−1.000	.000	−1.000	−1.000	
−1.0	−.447	.240	−.521	−1.921	
−.9	−.410	.262	−.475	−2.103	
−.8[a]	−.371	.286	−.428	−2.334	
−.7	−.330	.310	−.379	−2.636	
−.6	−.287	.336	−.329	−3.043	
−.5[a]	−.243	.362	−.276	−3.619	
−.4	−.196	.389	−.223	−4.490	
−.3	−.148	.416	−.168	−5.953	
−.2[a]	−.100	.444	−.112	−8.892	
−.1	−.050	.472	−.056	−17.739	
0[a]	.000	.500	.000	∞	∞
.1	.050	.528	.056	17.739	1,220
.2[a]	.100	.556	.112	8.892	306
.3	.148	.584	.168	5.953	139
.4	.196	.611	.223	4.490	107
.5[a]	.243	.638	.276	3.619	61
.6	.287	.664	.329	3.043	39
.7	.330	.690	.379	2.636	26
.8[a]	.371	.714	.428	2.334	20
.9	.410	.738	.475	2.103	16
1.0	.447	.760	.521	1.921	13
∞	1.000	1.000	1.000	1.000	∞

A sample size necessary to achieve 80% or more power with a 5% one-tailed test is also presented. AUC, area under the receiver operating characteristic curve; SRD, success rate difference; NNT, number needed to treat.

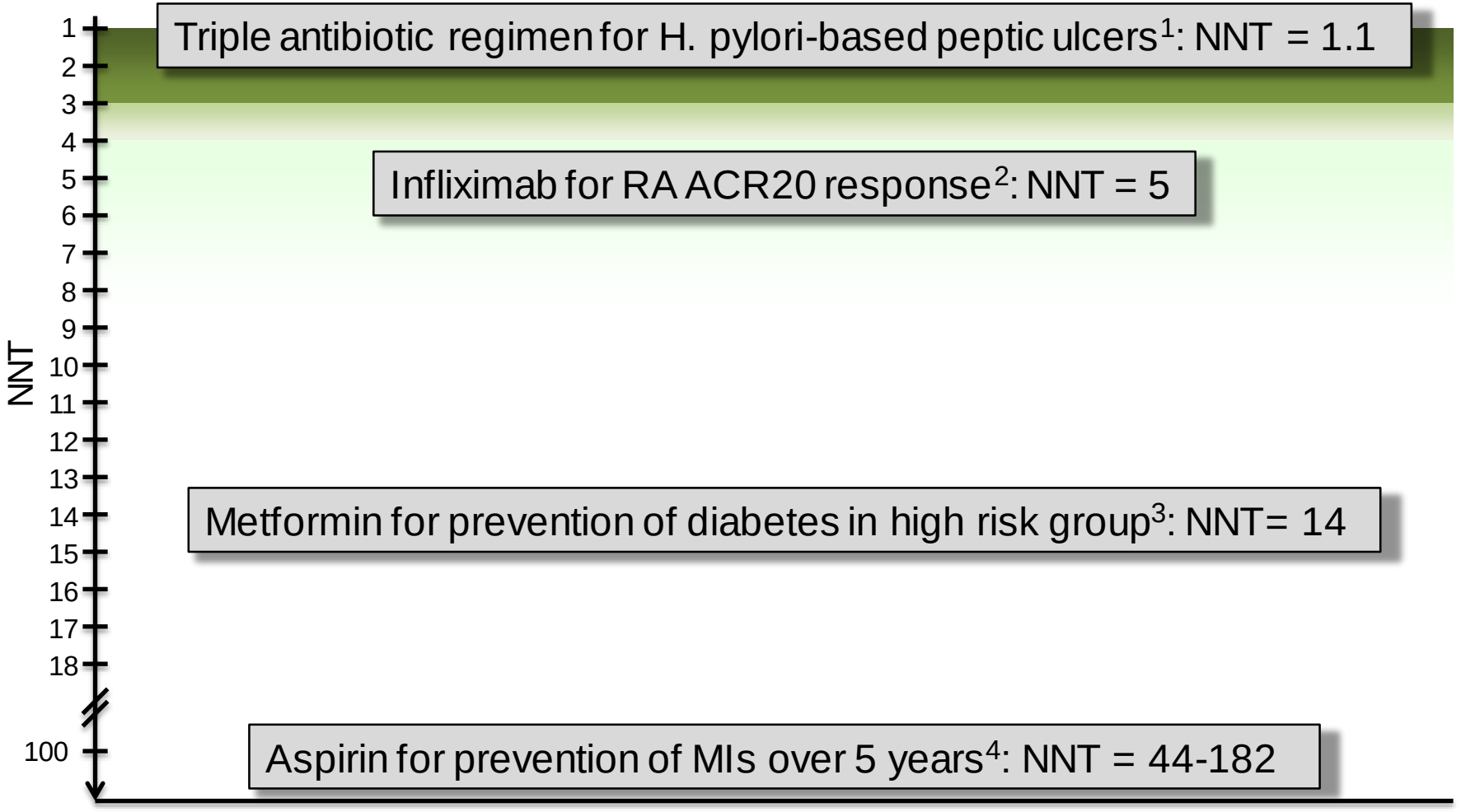
[a]Cohen's suggestions for "small," "medium," and "large" effect sizes (positive when treatment is better than control, negative otherwise).

* Kraemer HC, Kupfer DJ. Size of Treatment Effects and Their Importance to Clinical Research and Practice. *BIOL PSYCHIATRY 2006;59:990–996*

What Are Our Hopes?



What Are Some Precedents?



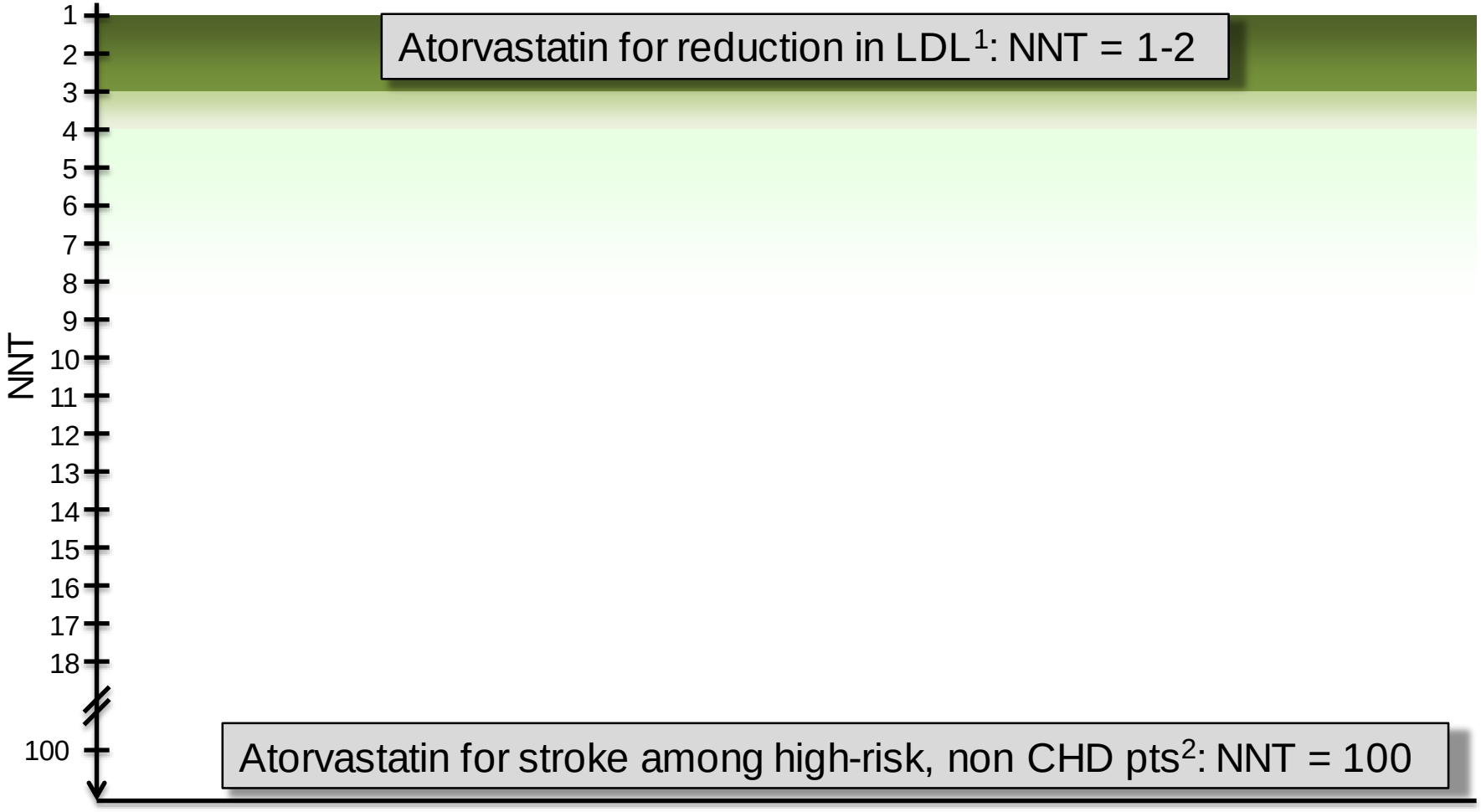
1 McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. Ann Intern Med 1997; 126: 712–720

2 Alonso-Ruiz et al., BMC Musculoskeletal Disorders 2008, 9:5

3 Gruber, A., Nasser, K., Smith, R., Sharma, J. C. and Thomson, G. A. (2006), Diabetes prevention: is there more to it than lifestyle changes?. International Journal of Clinical Practice, 60: 590–594.

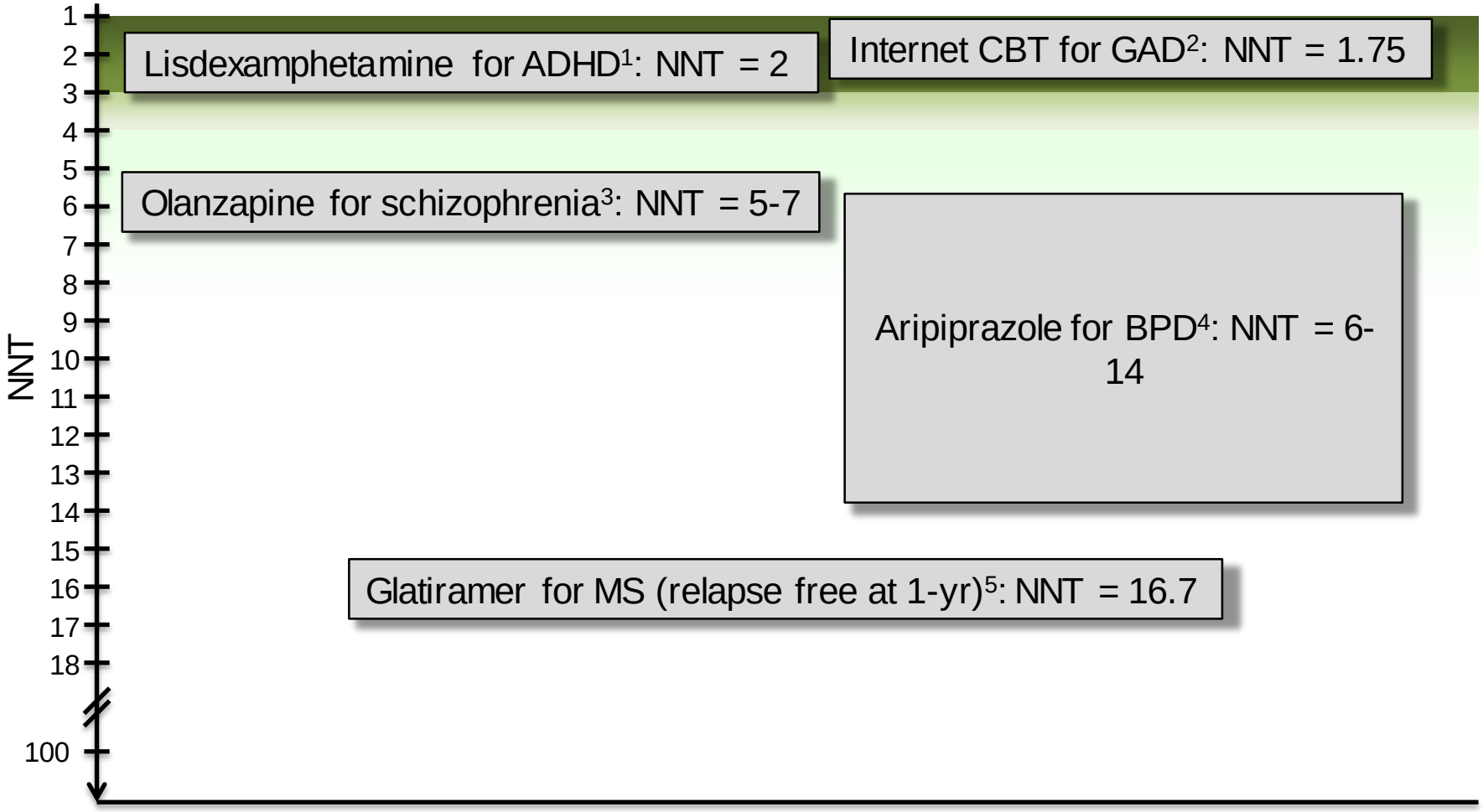
4 Sanmuganathan et al., Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials *Heart* 2001;85:265-271.

Endpoints Matter



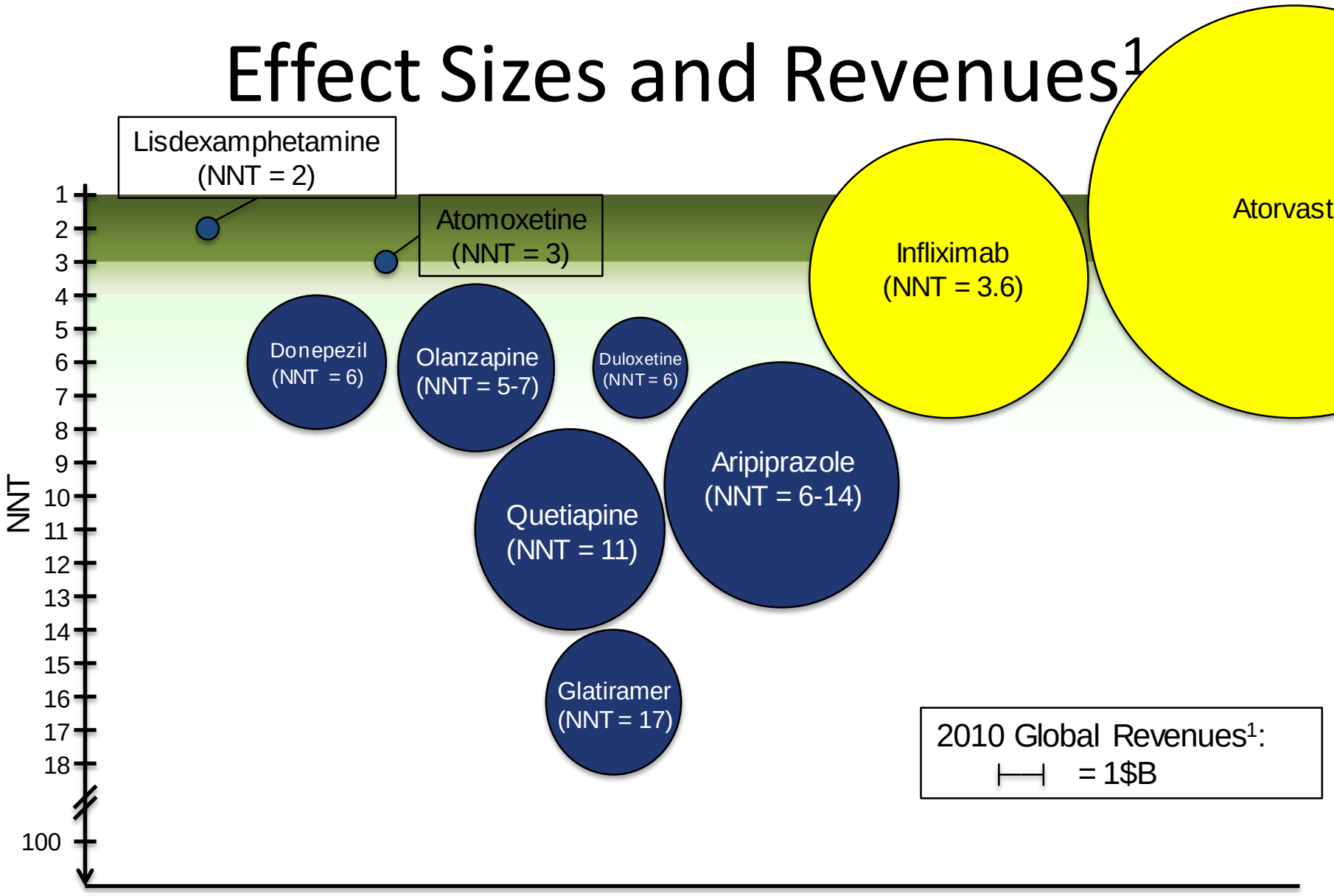
1 http://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020702_s000.pdf
2 http://www.medicine.ox.ac.uk/bandolier/booth/cardiac/statascot.html

How do CNS Therapies Compare?



1 Meszaros et al., International Journal of Neuropsychopharmacology (2009), 12, 1137–1147
2 Andrews G, Cuijpers P, Craske MG, McEvoy P, Titov N (2010) Computer Therapy for the Anxiety and Depressive Disorders Is Effective, Acceptable and Practical Health Care: A Meta-Analysis. PLoS ONE 5(10)
3 Cochrane review: Olanzapine for schizophrenia (Review) (2011)
4 Fountoulakis et al. J Affect Disord. 2011 Oct;133(3):361-70. Epub 2010 Oct 30
5 Freedman et al., Eur Neurol 2008;60:1–11

Effect Sizes and Revenues[1]



1 Maggon, Krishan; Guild (KPG), Knol Publishing. Top Ten/Twenty Best Selling Drugs 2010:World Best Selling Human Medicinal Brands 2010, Top Ten, Top Twenty, First Global Market Report [Internet]. Version 70. Knol. 2011 Nov 10. Available from: http://knol.google.com/k/krishan-maggon/top-ten-twenty-best-selling-drugs-2010/3fy5eowy8suq3/141.

Aims of the Panel

- Define 'clinically meaningful effect' from the perspective of important stakeholders
  - Consumers
  - Payers
  - Health care economists
  - Investors
- Gain regulatory perspective from FDA and EMA representatives
- Gather expert statistical recommendations regarding innovative strategies for defining clinically meaningful effect for RCTs.
- Panel discussion