

Pragmatic Studies

Why do payers care?

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Payers appreciate what explanatory trials with innovative agents have brought us
but also where unmet needs remain....

MI rates

- 28 in 1997
- 19.2 in 2007

Hip Fx rates

- 87.9
- 69.6

Mental disorder rates

- 72.6
- 79.4

Source: National Hospital Discharge Surveys 1997 and 2007. Age and sex adjusted Hospitalization rates per 10,000 – hip fracture only examining those >65.

Payer perspective

- Explanatory trials are necessary.....
- But not sufficient

Payers and their healthcare administrators: decisions at launch

- Formulary – cover or no, what tier?
 - *Compared to other drugs or other interventions....*
- Prior authorization – who should or should not get the drug?
 - *Sub-populations?*
 - *Companion diagnostic?*
- Use limitations – for what duration does the product work? Are there concomitant services required?
 - *Quantity limits – how long should a drug be taken?*
 - *Step therapies – try drug A before drug B*
 - *Monitoring? – something special?*
 - *Special conditions of where care needs to be provided?*

Without comparative data, what are payers forced to do?

- Meta-analysis or systematic reviews ***across*** placebo controlled trials of competing products
- Problems ...
 - differing study protocols,
 - different definitions of endpoints,
 - differing durations of treatment,
 - differing conditions of study, etc etc.....

Example: Crohn's disease drugs (2 popular TNF alphas)

- DARE (Database of Abstracts of Reviews of Effects)
 - MEDLINE, EMBASE, and Cochrane Register up to 2007
 - Conference abstracts 2006 and 2007
 - EMA and FDA
 - Industry submissions
- ALL BUT 2/11 TRIALS COMPARED EACH DRUG WITH PBO
- “Due to clinical heterogeneity, the studies were combined in a narrative synthesis.....”

Source: Dretzke J et al: A systematic review and economic evaluation of the use of TNF alpha inhibitors, adalimumab and infliximab for Crohn's disease. Health Tech Assess 2011;15(6):1-244.

When IOM announced new funding for pragmatic trials
(CER studies)

Pent up demand! People do care!

- >2600 topic areas submitted
- In only 3 week time window for submissions
- >1700 submitters
- Winnowed down to 29 topic areas (100 issues)
<http://www.iom.edu/~media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/CER%20report%20brief%2008-13-09.pdf>

We've heard from today's speakers..
Some of the attributes of these studies

- More representative populations of patients
- Active comparators
- Self-reported and hard endpoints
- More naturalistic settings of care

Representative Populations

- Parkinson' Disease in the community
 - 36.3% have heart/circulation problems*
- Yet.....typical explanatory trials have exclusion criteria “any form of clinically significant CV disease” and even just hypertension noted on two pre-qualification visits.....**

Sources:

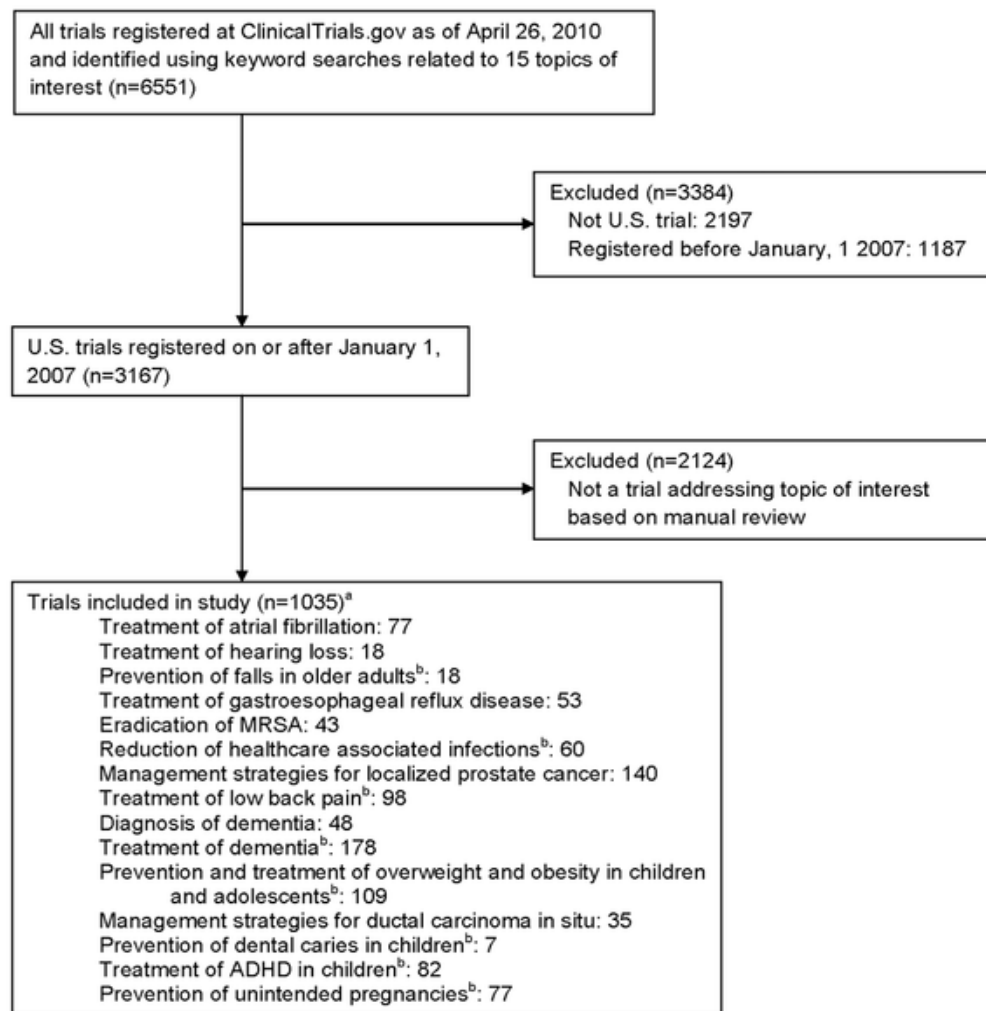
1. Jones JD: Health comorbidities and cognition in 1947 patients with idiopathic Parkinson's disease. Park Relat Disord 2012:july 7:epub ahead of print
2. Review of 82 ongoing Phase 3 Parkinson's trials on www.clinicaltrials.gov 9/2012.

Payers would then wonder.....

- What about the 1/3 of my population who have significant heart disease?
- Will the new drug make the underlying CV problem worse?
- Will there be drug interactions to worry about? – Could the CV drug actually influence the Parkinson's drug effects or vice versa?

Active comparators

ELEGANT STUDY OF 15/25 Topics chosen by IOM



Bourgeois FT, Murthy S, Mandl KD (2012) Comparative Effectiveness Research: An Empirical Study of Trials Registered in ClinicalTrials.gov. PLoS ONE 7(1): e28820. doi:10.1371/journal.pone.0028820

<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0028820>

Only 22.3% of trials covering topics deemed important by IOM – had active comparators

RESULTS

- 231 (22.3%) had active comparators
- 379 (36.6%) compared with PBO
- 45 (41.1%) no control

MS Drugs Being Evaluated in Phase 3

- I accessed www.clinicaltrials.gov 9/2012
- 99 studies recruiting or about to recruit for Phase 3 studies of M.S.
- 16/99 (**16%**) have an active comparator (remainder have placebo or no control)

Do we only want to think about Drug A vs Drug B?

EXAMPLE OF PREDIABETES – MAY WANT TO THINK OF EARLY COGNITIVE STUDIES

- Estimated 30-35% will develop frank diabetes within 3 years
- Database research (n=144,410 pts tracked longitudinally) has suggested
 - Those who developed DM - \$1429 more expensive in Yr1, \$2451 in Yr2, and \$3621 in Yr3
 - Not to mention productivity and HR-QoL issues

Source: Francis BH et al: Progression to type 2 diabetes, healthcare utilization, and cost Among pre-diabetic patients with or without comorbid hypertension. Curr Med Res Opin 2011;Apr 27(4);809-819.

The Diabetes Prevention Program

A Randomized Clinical Trial
to Prevent Type 2 Diabetes
in Persons at High Risk

The DPP Research Group



DPP Primary Goal

- To prevent or delay the development of type 2 diabetes in persons with impaired glucose tolerance (IGT)

Study Design

- 3-group randomized clinical trial
- 27 clinical sites
- Standardized across clinics:
 - Common protocol and procedures manual
 - Staff training
 - Data quality control program

Eligibility Criteria

- Age \geq 25 years
- Plasma glucose
 - 2 hour glucose 140-199 mg/dl (7.8- <11.1 mmol/L)
 - and
 - Fasting glucose 95-125 mg/dl (5.3- <7.0 mmol/L)
- Body mass index \geq 24 kg/m²
- All ethnic groups
 - goal of up to 50% from high risk populations

Study Interventions

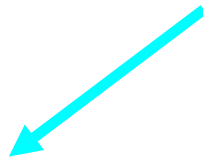
Eligible participants



Randomized



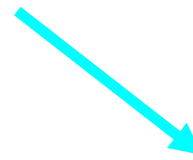
Standard lifestyle recommendations



**Intensive
Lifestyle**
(n = 1079)



Metformin
(n = 1073)



Placebo
(n = 1082)

Effect of Treatment on Incidence of Diabetes

	<u>Placebo</u>	<u>Metformin</u>	<u>Lifestyle</u>
<u>Incidence</u> of diabetes (percent per year)	11.0%	7.8%	4.8%
<u>Reduction</u> in incidence compared with placebo	----	31%	58%
<u>Number needed to treat</u> to prevent 1 case in 3 years	----	13.9	6.9

Payers especially care about

- Impact of comparative treatment on direct medical care costs
 - Inpatient stays, outpatient visits and labs/diagnostics, outpatient visits, medications
 - Total resource utilization downstream from treatment
 - When it comes to PROs (patient reported outcomes)....depends on payer appetite

Nifty example in COPD

Multivariate Regression Results

Propensity Score Matching Results

COPD related utilization	FSC N=12595	TIO N=9126	P value	FSC N=8135	TIO N=8135	P value
OP visit	3615 (28.7%)	3661 (40.1%)	<0.001	2567 (31.6%)	3147 (38.7)	<0.001
OP with antibiotic	490 (3.9)	478 (5.2)	<0.001	355 (4.4)	402 (4.9)	0.08
OP with steroid	261 (2.1)	262 (2.9)	0.001	178 (2.2)	224 (2.8)	0.02
ED visit	450 (3.6)	427 (4.7)	<0.001	277 (3.4)	366 (4.5)	<0.001
Hosp	446 (3.5)	413 (4.5)	<0.001	314 (3.9)	343 (4.2)	0.25
Hosp/ED visit	819 (6.5)	764 (8.4)	<0.001	544 (6.7)	647 (8.0)	0.002

Source: Roberts MH, Dalai AA: Clinical and economic outcomes in an observational study Of COPD maintenance therapies: multivariate regression vs. propensity matching. Int J Chron Obstruct Pulmon Dis 2102:7;221-223.

Settings and conditions of care...

Re-look at that pre-diabetes A-ha

- In 2008, Dutch Ministry of Health funded lifestyle program for prediabetics
- BeeweegKuur:
 - lifestyle coach,
 - one of 3 physical activity programs,
 - consult with dietician

Results at 1 year

Propensity matched comparison

- No significant difference in fasting glucose at 1 year or HbA1c
- No significant difference in BMI, BP, cholesterol, LDL, HDL or triglycerides

CONCLUSIONS

- Payers truly appreciate the explanatory trial data particularly with breakthrough treatments
- Pragmatic trials answer many more of their questions
 - Compared to what else they pay for today
 - Among ‘real world’ patients with comorbidities
 - Under typical treatment conditions
 - With endpoints that matter most to them

THANKS FOR THE OPPORTUNITY TO
PARTICIPATE