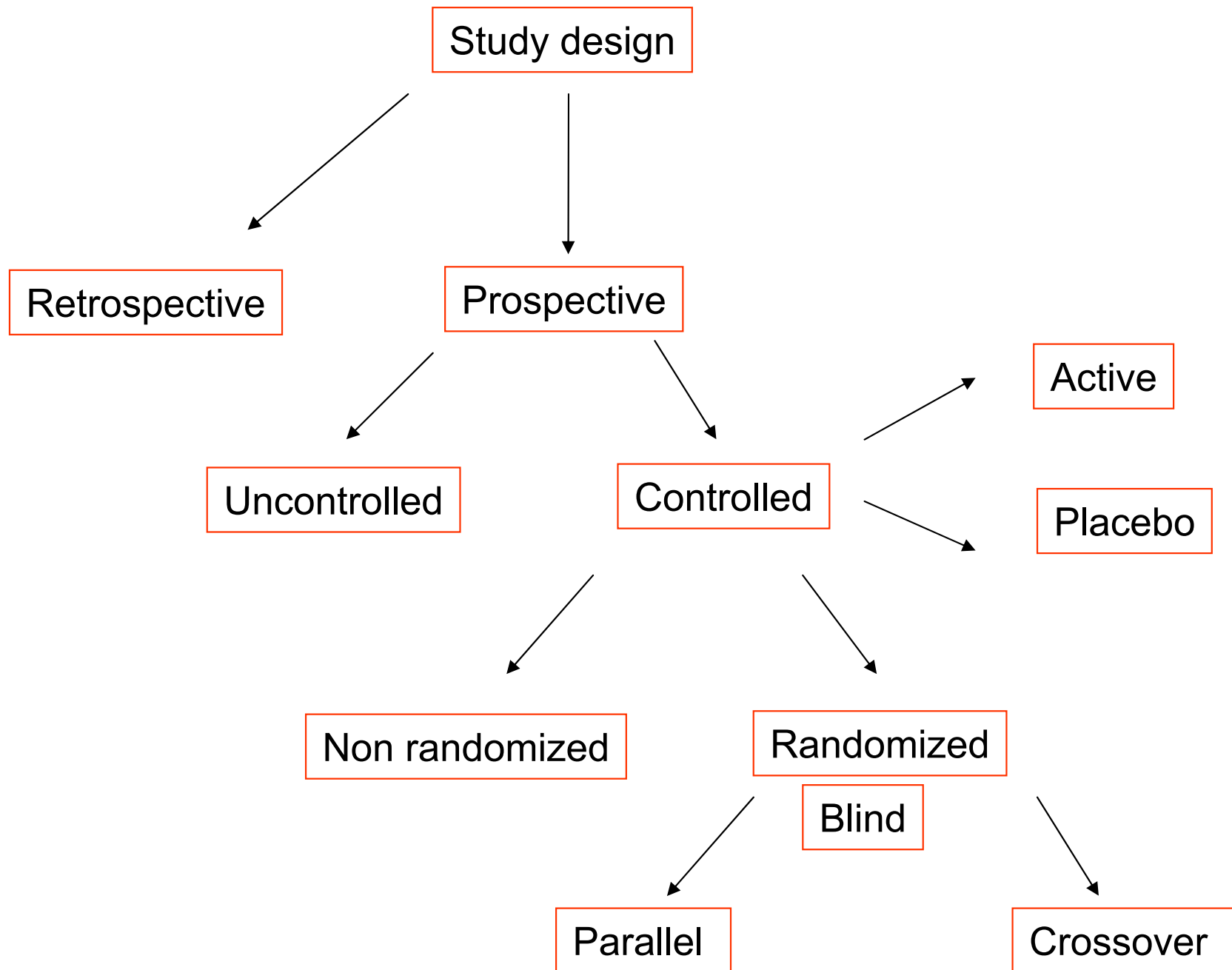# Introducing new research results in daily clinical practice: how much evidence do we need to implement research into practice?

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                        │ Study design│
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Controlled clinical trials in cancer pain: how controlled should they be? A qualitative systematic review.
Bell et al, Br J Cancer 2006

- Multicenter v single trials: 80 v 40
- 26 CO, 8 parallel design, 26 DD technique, 33 equivalency studies
- Group size => 20
- Duration 7-14 days
- Withdrawal 10-30% (AE, deterioration, poor pain relief)
- Sponsored 24/36

- Define good and bad responders
- Identify factors that influence the outcome

Equivalency studies… often sponsored

Do not measure efficacy directly.

Need more patients to produce reliable conclusions

Same result with three different conclusions:

- Both treatments are effective
- Both treatments are equally ineffective
- Inadequate to detect differences

Placebo control

- Ethically acceptable?

Provide rescue doses… and rescue medication gets the primary outcome

PCA analgesia is not equivalent to background medication…

Cross over or parallel?

- Patient preference..
- Low number of patients..
- Short for withdrawal
- Drug phase effect

- Simple
- Higher number of patients
- No identical population

Enriched enrolment

Screen

Titrate to effect

$\longrightarrow$

- Proportion of R-NR
- Optimal dose
- Withdrawal for adverse event lack of efficacy

Randomization

Active

Evaluation

Control
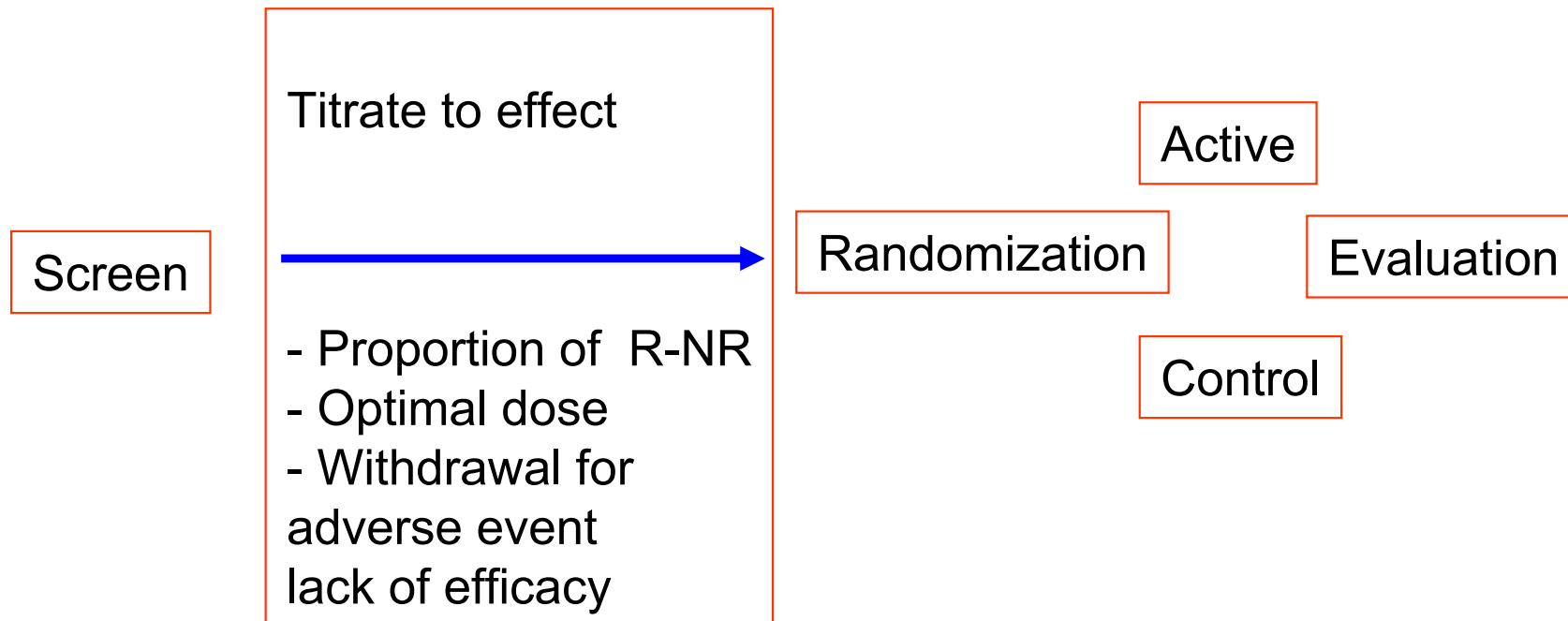
Efficacy and safety of transdermal buprenorphine. Poulain et al, 2008 JPSM

• Enriched design in 289 tolerant patients switched
to TS BP 70 μg/h in a two week run-in phase
• 189 pts entered maintainance phase versus placebo.
• Sublingual BP as needed
• Primary oucome: % of pts with PI<5, with 2 tablets as needed

Results:
74% TS BP versus 50% placebo
Better PI and stable tablet consumption with TS BP
Better global satisfaction (no significant)

Artificial context

- Realistic scenario?
- Reliable data?

- Effects of PRN medication as substitute of background medication?
- Fixed background doses as for protocol…

- Pts with placebo have 50% chances for success
- Pts treated have 75% chances for success
- Can we say that is effective?

Katz N, Methodological issues in clinical trials of opioids for chronic pain. Neurology 2005

Failure of a clinical trial to demonstrate a difference between analgesic and placebo when there is every reason to believe that the drug is truly efficacious. Factors limiting failure:

- ✓ Slow titration of medication
- ✓ Flexible dosing
- ✓ Minimizing concomitant and rescue analgesic
- ✓ Homogeneous sample
- ✓ Fewer study sites

✓ Limited RCT evidence supports EAPC cancer pain management guidelines

✓ RCT evidence refutes guidelines on breakthrough management and neuropathic pain

- Morphine as first line opioid
- Recommendations about titrating with immediate release morphine
- Nightly double dose of immediate release morphine
- No predictable relationship between BP and AC doses
- No evidence for opioid switching for AE
- Single and multiple fraction RT are equianalgesic
- Bisphosphonates, radiotherapy and radioisotopes: heterogeneity of trial design, pain definition and evaluation, short study duration, lack of pain classification and limited AE reporting

B - Opioid titration in pts no longer responsive to II step opioids

EAPC recommendations: during dose titration it is preferable to use IR morphine that has a rapid onset, a predictable effect, and a short duration of action to allow steady state to be achieved as quickly as possible.

 A dose of IR oral morphine is given every 4 hours and the same dose for BP given as often as required.

Pts changing from a weak opioid will usually start with 10 mg every four hours (60 mg/day), while if step two of the analgesic ladder is omitted 5 mg every four hours may suffice.

The total daily dose of morphine should be reviewed daily, based on the assumption that steady state of morphine is reached in about 24 hours. If pain returns before giving the regular dose, the regular dose should be increased (Hanks et al, 2001).

PAIN INTENSITY AND SIDE EFFECTS DURING TITRATION OF MORPHINE TO CANCER PATIENTS USING A FIXED SCHEDULE DOSE ESCALATION

Klepstad P. et al, Acta Anaesthesiol Scand 2000

40 pts on 2nd step: 2 days ketobemidone as needed

IR morphine for each day titration: 10 mg x 6, 15 mg x 6, 20 mg x 6, 30 mg x 6, 45 mg x 6

After stabilization: SR morphine

Titration time 2.3 days (1-6)

Dose 97 mg (60-180)

Pain 32 (pre-morphine) →18 (post-titration)

Vomiting 29%

Sedation delayed dose increment in 9/40 pts

Constipation

82% satisfied

Recommendations about titrating with immediate release morphine

Klepstad et al, Immediate- or sustained-release morphine for dose finding during start of morphine to cancer patients: a RC-DB trial. Pain 2003

- A titration procedure using immediate-release morphine given 4-hourly is recommended during start of oral morphine for cancer pain. This recommendation is not based on evidence from controlled studies, and many physicians start morphine treatment with controlled-release morphine.
- 40 pts on opioids for mild to moderate pain unsuccessfully.
- Randomized, DB-DD, parallel-group study comparing IR morphine given 4-hourly and SR morphine given once daily.
- The mean times needed for titration were 2.1 days using IR morphine and 1.7 using SR morphine.
- Patients titrated with immediate-release reported statistically significant more tiredness at the end of titration.
- Similar global satisfactions with the morphine treatments were reported.
- A simplified titration using sustained-release morphine once daily is equally effective as immediate-release morphine given 4-hourly.

Opioid of choice

Mercadante et al, Eur J Pain 2008: 108 pts randomly received initial daily doses of 60mg of oral sustained-release morphine, 15mg of oral methadone, or 0.6mg (25μg/h) of TTS fentanyl:

➢ Similar opioid switching rate.
➢ No differences in pain intensity were observed.
➢ OEI lower with methadone(<morphine<fentanyl), but up and down changes in doses.
➢ Methadone less expensive
➢ Supportive care drugs consumption similar
➢ Less AE with TTS fentanyl, more expensive
➢ All the three opioids used as first-line therapy were effective, well tolerated, and required similar amounts of symptomatic drugs or co-analgesics. Methadone was significantly less expensive, but required more changes, up and down, of the doses, suggesting that dose titration of this drug requires major clinical expertise.

Opioid of choice

☐ Reid et al, Ann Intern Med 2004:

Four studies, comparing oral oxycodone with either oral morphine or oral hydromorphone, were suitable for meta-analysis.

The efficacy and tolerability of oxycodone are similar to morphine, supporting its use as an opioid for cancer-related pain.

Titration 2: Conclusion

Doses of about 60 mg of oral morphine equivalents of any opioid, are equally effective as starting doses in pts who had received step 2 drugs unsuccessfully….

PRN opioid doses for assisting titration

- Morphine   60
- TTS fentanyl   0.6 (25 µg/h)
- Methadone   15
- Oxycodone   40
- TTS buprenorphine   0.8 (35 µg/h)
- Hydromorphone   12

Assisting opioid titration when using slow preparations:
SR morphine, SR oxycodone, methadone, transdermal drugs: fentanyl and buprenorphine

- 1/6 of the daily dose as equivalents of oral morphine (also useful as BP medication)

EAPC RECOMMENDATION:
give a DD at bedtime instead of SD at 10 PM and 2 AM, based on clinical sense. No evidence 🙁

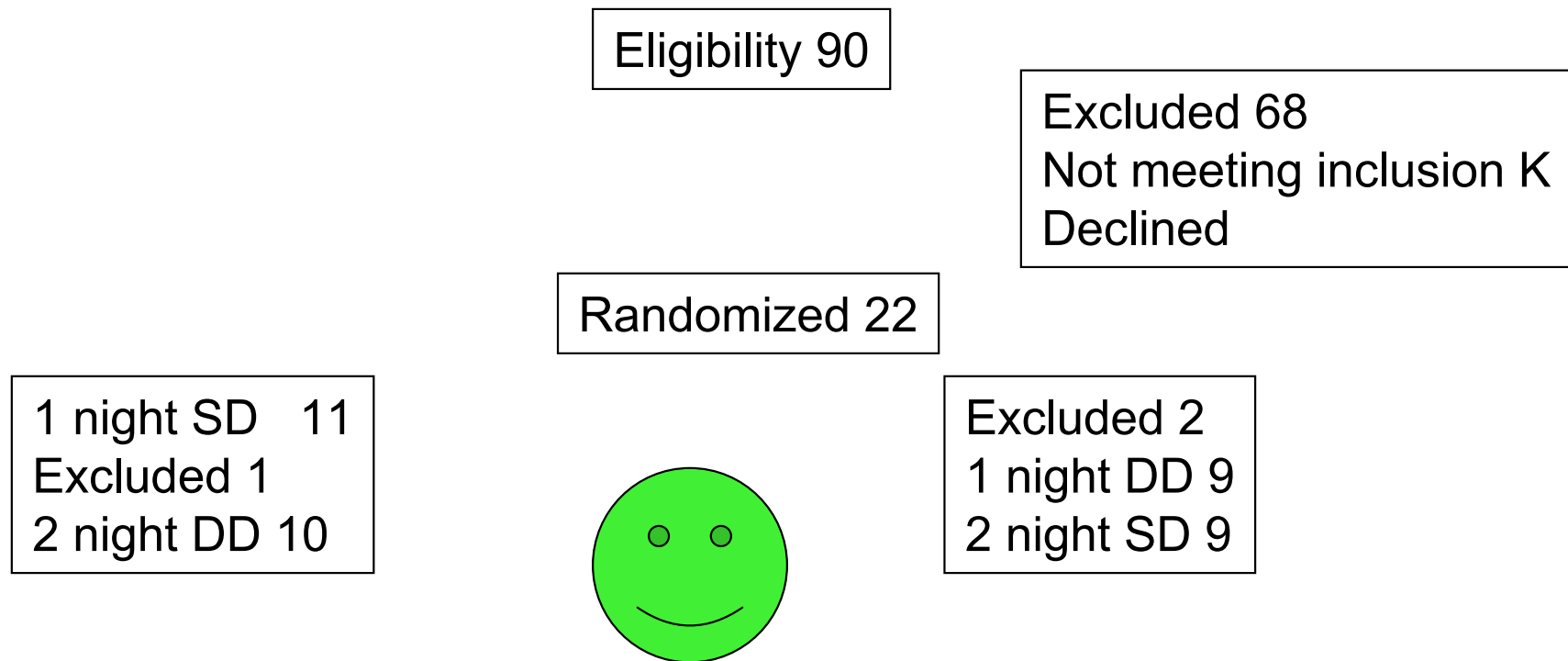- Todd et al,Palliat Med 2002

Design: open, CO, randomized, 20 pts

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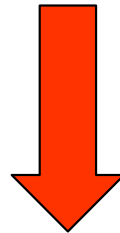
DD more pain, more rescue medications, more AE

Patient preference is better than any evidence

- Do you prefer to be woken up at 2:00 AM?

I' ll phone tonight….

- May be do you prefer to not be woken up

A double blind randomized clinical and pharmacokinetic comparison between double-dose of immediate morphine versus single-dose morphine at bedtime to cancer patients.
Dale et al, J Pain Symptom Manage

Eligibility 90

Excluded 68
Not meeting inclusion K
Declined

Randomized 22

1 night SD   11
Excluded 1
2 night DD 10

Excluded 2
1 night DD 9
2 night SD 9

DD tended to perform slightly better, regardless the possible advantage of not being awaked at night.

Clinical significance of M6G?

OTFC has been shown to be more rapid and effective than oral morphine, which has been so far considered the goal standard for breakthrough pain, and its onset is similar to that IV morphine
Enrichment enrolment

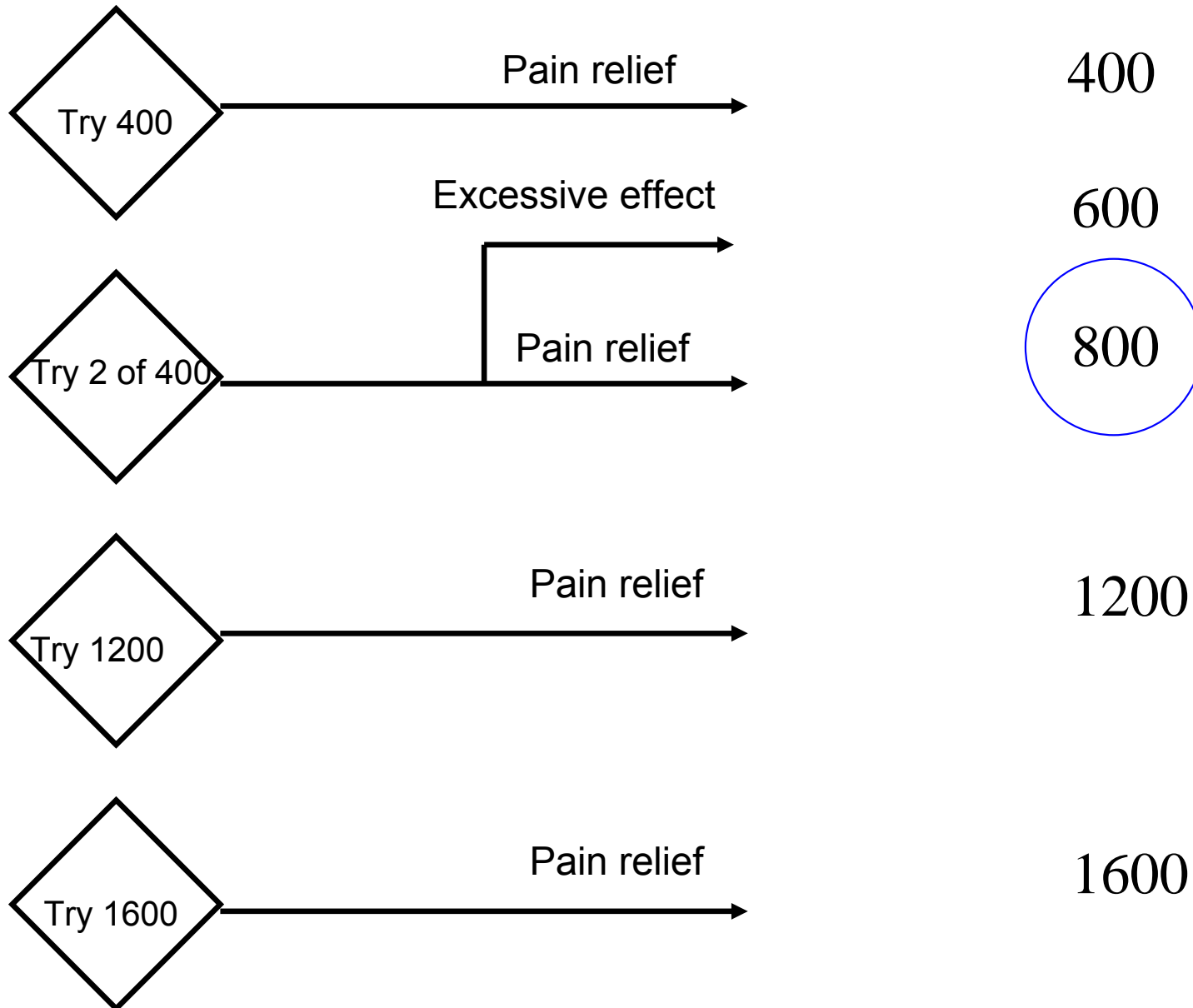Despite the obvious practical implication, some questions remained unclear and should solved in appropriate studies:

 Lack of relation between basal dose and dose as needed…
The need to titrate….
 Practical limitations…

Starting and titrating OTFC
Aronoff et al, Pain Med 2005

✓ Portenoy RK, et al. *Pain*. 1999;79:303-312.
✓ Christie JM, et al. *J Clin Oncol*. 1998;16:3238-3245.
✓ Farrar JT, et al. *J Natl Cancer Inst*. 1998;90:611-616.
✓ Coluzzi PH, et al. *Pain*. 2001;91:123-130.

Main concerns about OTFC studies in breakthrough pain

➤ BP type ? Incident ? Activity test?

➤ 66% of the episodes with placebo did not require additional dose medication (short-lived episodes? Placebo response?)

➤ Basal pain controlled (4 episodes/day)?

➤ BP not severe enough Mean basal pain 4.7 (with extremes 1-9)

➤ Mean breakthrough pain: 6.8 (with extremes 2-10)

Practical issues

What do we expect from 200 mcg of OTFC in a patient

receiving 240 mg of oral morphine as basal medication?

    a) Pain relief similar to placebo or any drug   50%

    b) Patient seriously angry: 50%

What do we expect from 800 mcg of OTFC in a patient

receiving 240 mg of oral morphine as basal medication?

    a) Pain relief similar to placebo or any drug   50%

    b) Pain relief, patient satisfied   45%

    c) Patient unsatisfied   5%

    d) Patient seriously angry   0%

Dose of breakthrough oral opioid versus ATC dose
Significant relationship (p<0.001)

Hagen et al. J Palliat Med 2007
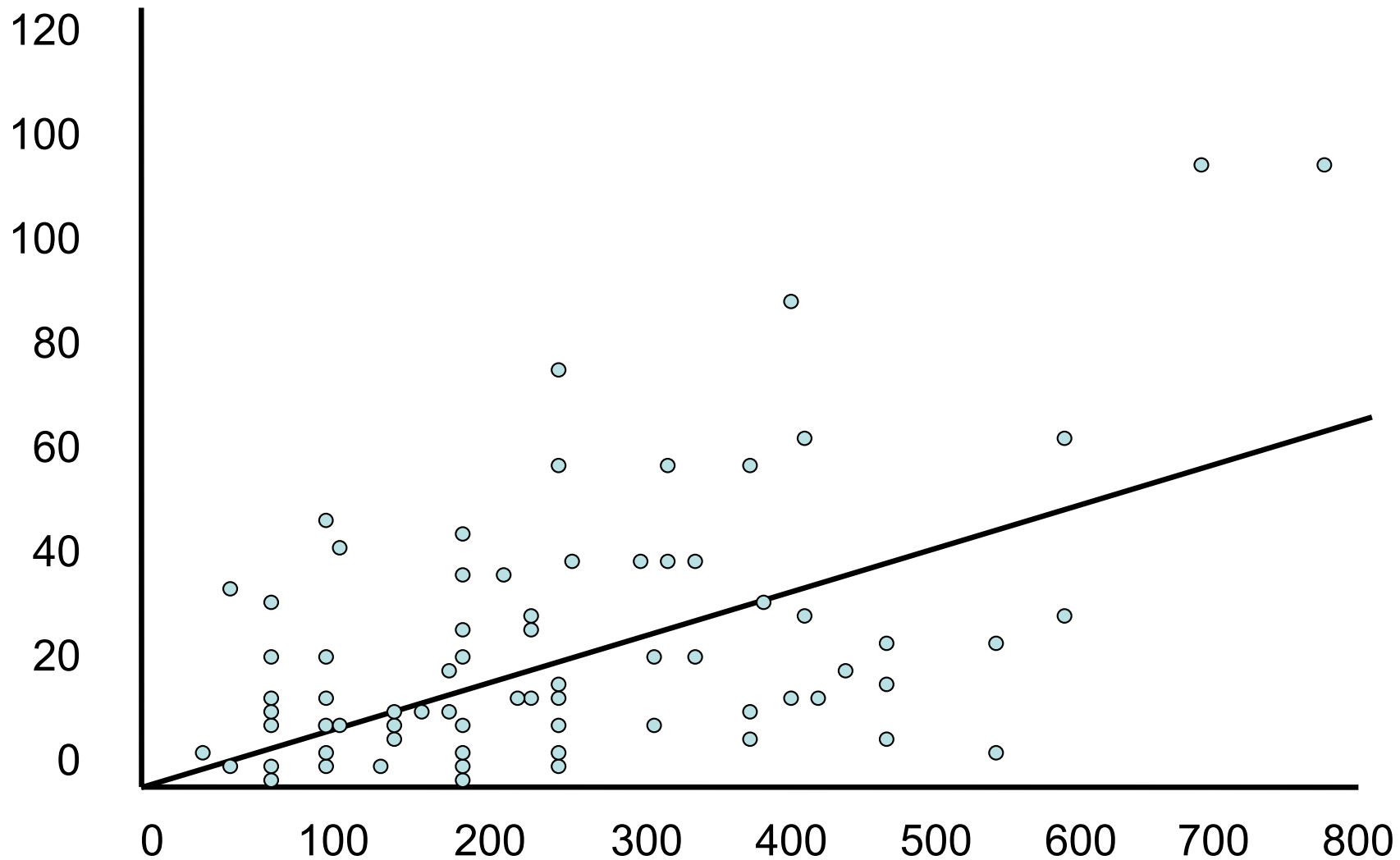
OTFC VERSUS IV-MORPHINE FOR EPISODIC-BREAKTHROUGH PAIN
S. Mercadante et al, Br J Cancer 2007

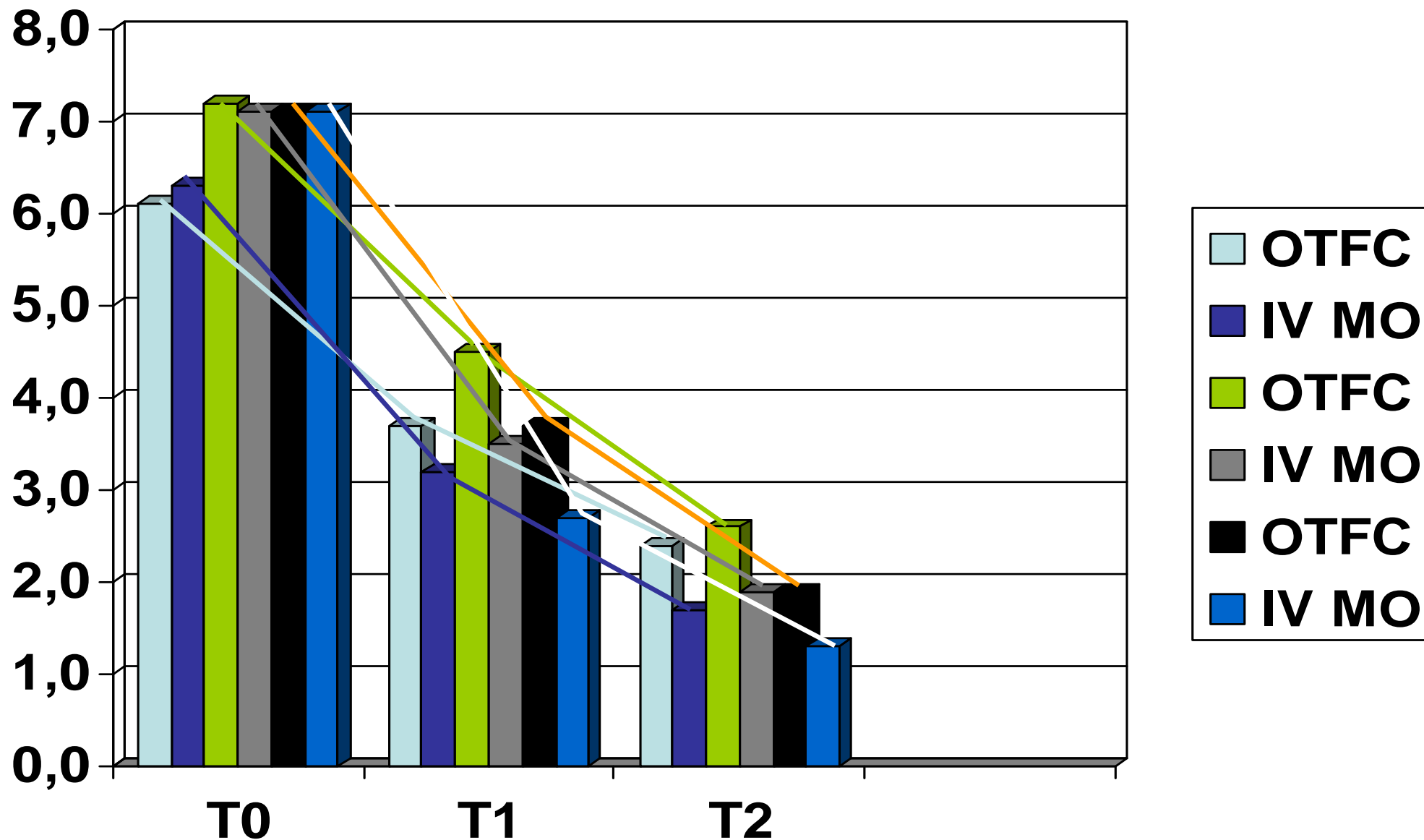|	
N° patients	25
Age	59 (55-63)
Gender (M/F)	12/13
Basal morphine dose	120 mg (96-144)
Doses (OTFC / IV-MO)	events / patients
200 / 4	9 / 6
400 / 8	5 / 3
600 / 12	14 / 5
800 / 16	6 / 1
1200 / 24	13 / 8
1600 / 32	6 / 2
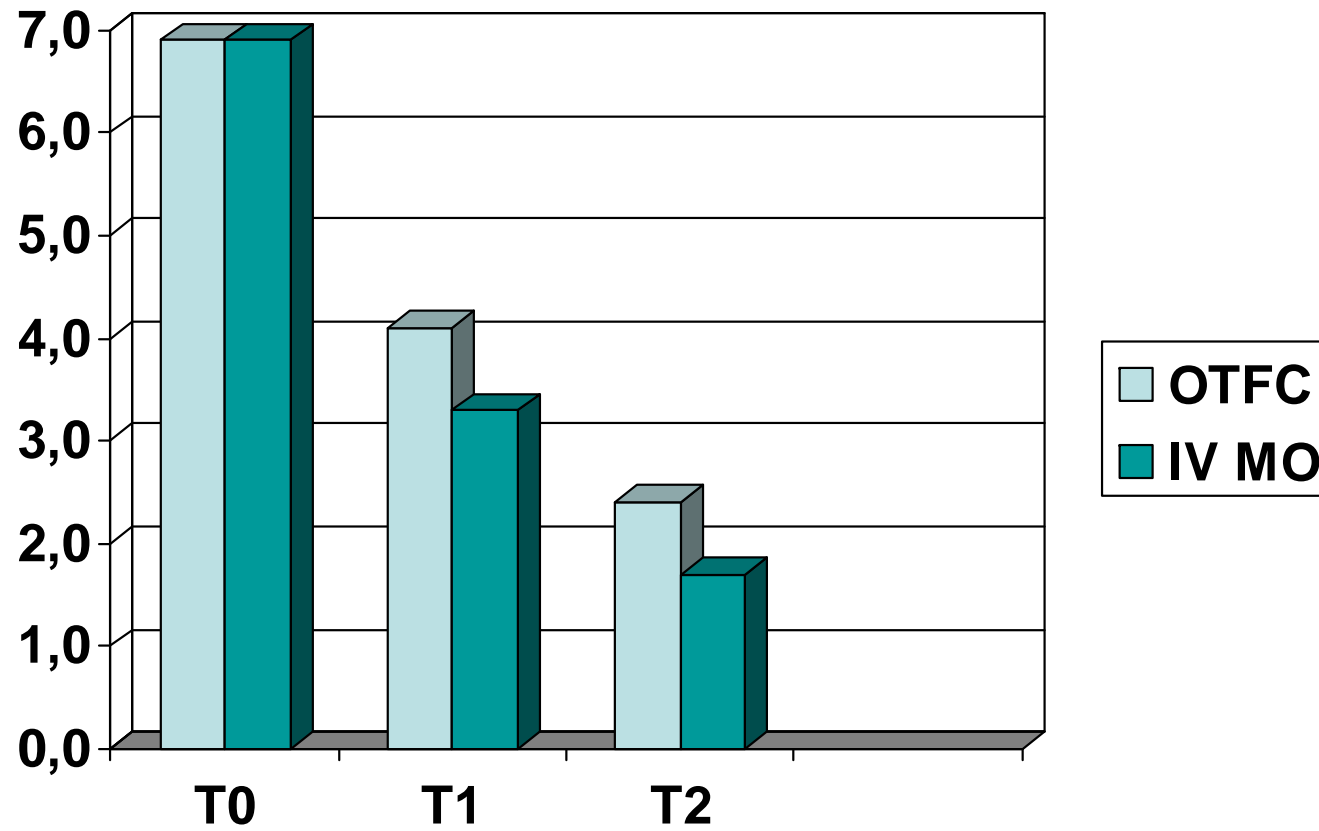
Table 2. Changes of pain intensity 15 (T1) and 30 minutes (T2) after treatment in all patients

Changes of pain intensity 15 and 30 minutes after treatment in patients using different ranges of basal opioid doses (<120 mg, 120-270 mg, >330 mg of oral morphine equivalents) . Data are expressed as mean

INTRAVENOUS MORPHINE FOR BREAKTHROUGH PAIN IN AN ACUTE PALLIATIVE CARE UNIT: A CONFIRMATORY STUDY.
Mercadante, et al JPSM 2008

Despite IV morphine is the fastest and potentially the most risky…

Even given in older pts or relatively large doses, IV-MO did not result in serious AE in a large number of episodes (945 events) while being effective by patients in most cases.

The mean dose of IV-M was 12 mg (95% CI 9-14 mg).
In 8 episodes no changes in pain intensity were observed and a further dose of IV-M was given. The remaining pts did not require further interventions.

No clinical event requiring medical intervention was recorded.

Use of opioids for BP at La Maddalena Cancer Center
Preliminary data on 425 episodes of BP from january 2008, in preparation

|	MO	FE	OX	BUP	MET
OTFC 200	60	0.6	40	0.8	12
IV MO 3.5					
Or MO 10					
OTFC 400	120	1.2	80	1.6	24
IV MO 7					
Or MO 20					
OTFC 600	180	1.8	120	2.4	36
IV MO 10.5					
Or MO 30					
OTFC 800	240	2.4	160	3.2	48
IV MO 14					
Or MO 40					

No emergency call

No evidence about opioid switching
Mercadante & Bruera, 2007

- Effective in 50-80% of unresponsive patients
- People are different
- Opioids are different
- Effective by chance…

Practical issues:
- Alternatives?
- Minimizing spinal therapy
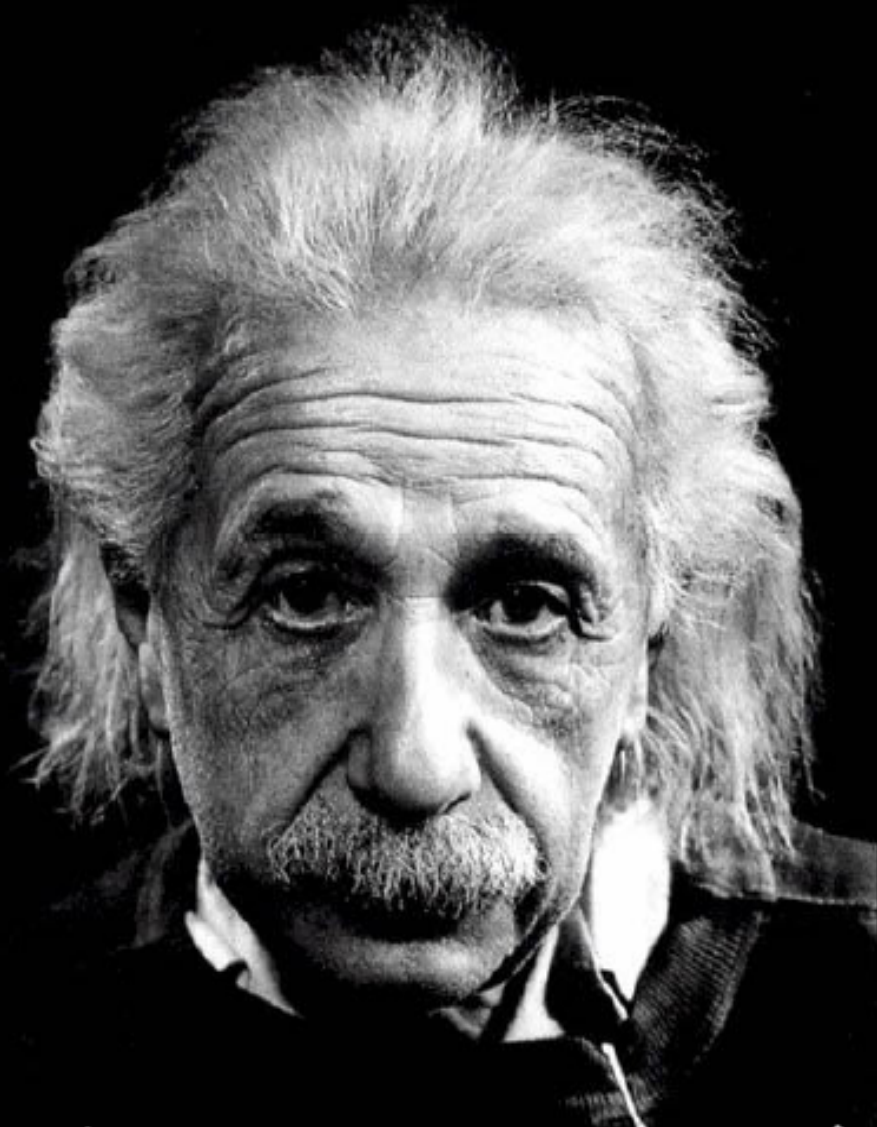
„NEVER STOP ASKING QUESTIONS"

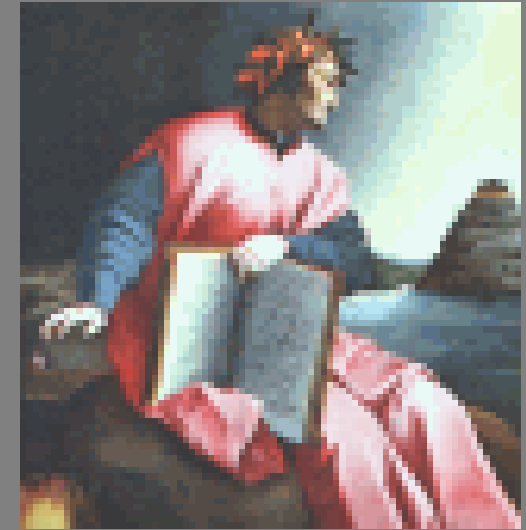# Protocols should reproduce the real world

- Eligibility
- End-points
- Stratification according to prognostic factors
- Stratification according syndromes
- Multivariate analysis
- Reasonable period of time
- Number of patients – interinstitutional trials

(not too many…)

26 canto, Inferno
Ulix to his sailor friends:

Dante Alighieri
La Divina
Commedia

"Fatti non foste a viver come bruti,

ma per seguir virtute e canoscenza"

You did not born to live as brute, but to pursue
 virtue and knowledge…