I devices dei farmaci respiratori
Quale ruolo nella scelta terapeutica?
Bologna 28 Settembre 2017

Gli Studi Clinici sui devices respiratori

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Presenter Disclosures

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Personal financial relationships with commercial interests relevant to medicine, within past 3 years**:**

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Devices respiratori: considerazioni generali

Devices respiratori: utilizzo e conseguenze

Studi Clinici: Confronto fra devices e patients' preferences

Studi Clinici: il paziente anziano

- **Disegno di uno studio**

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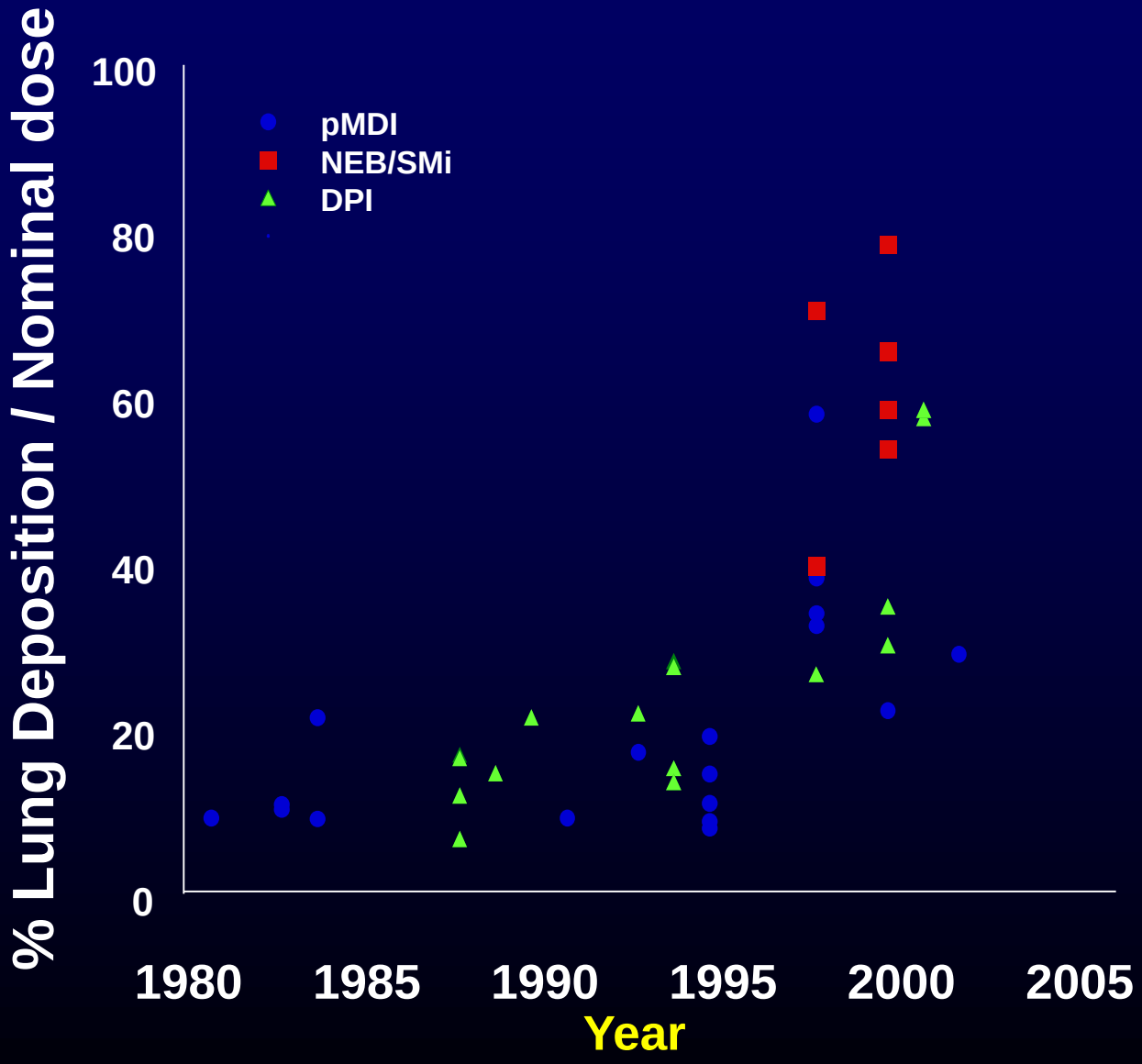
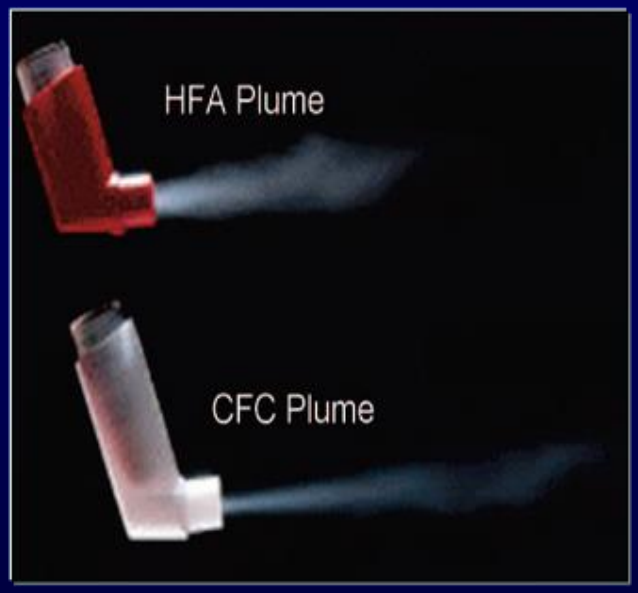
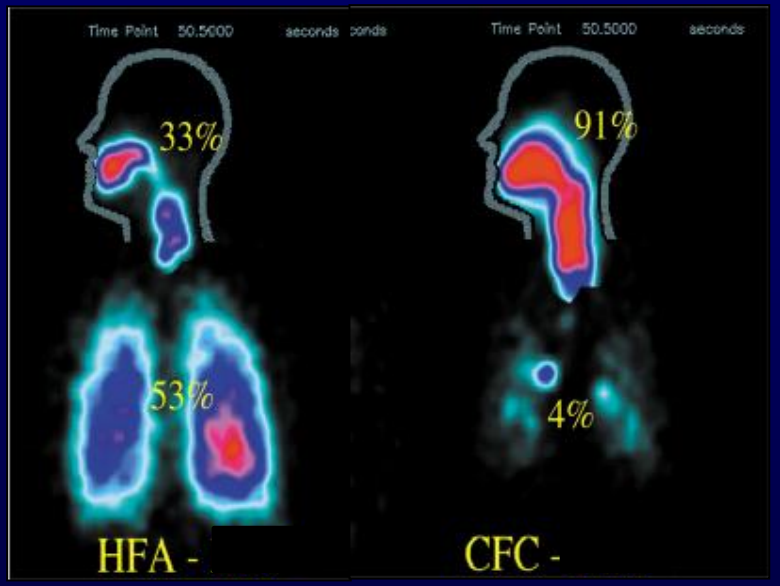
Improvements in Inhalation Delivery Efficiency 1980 - 2005



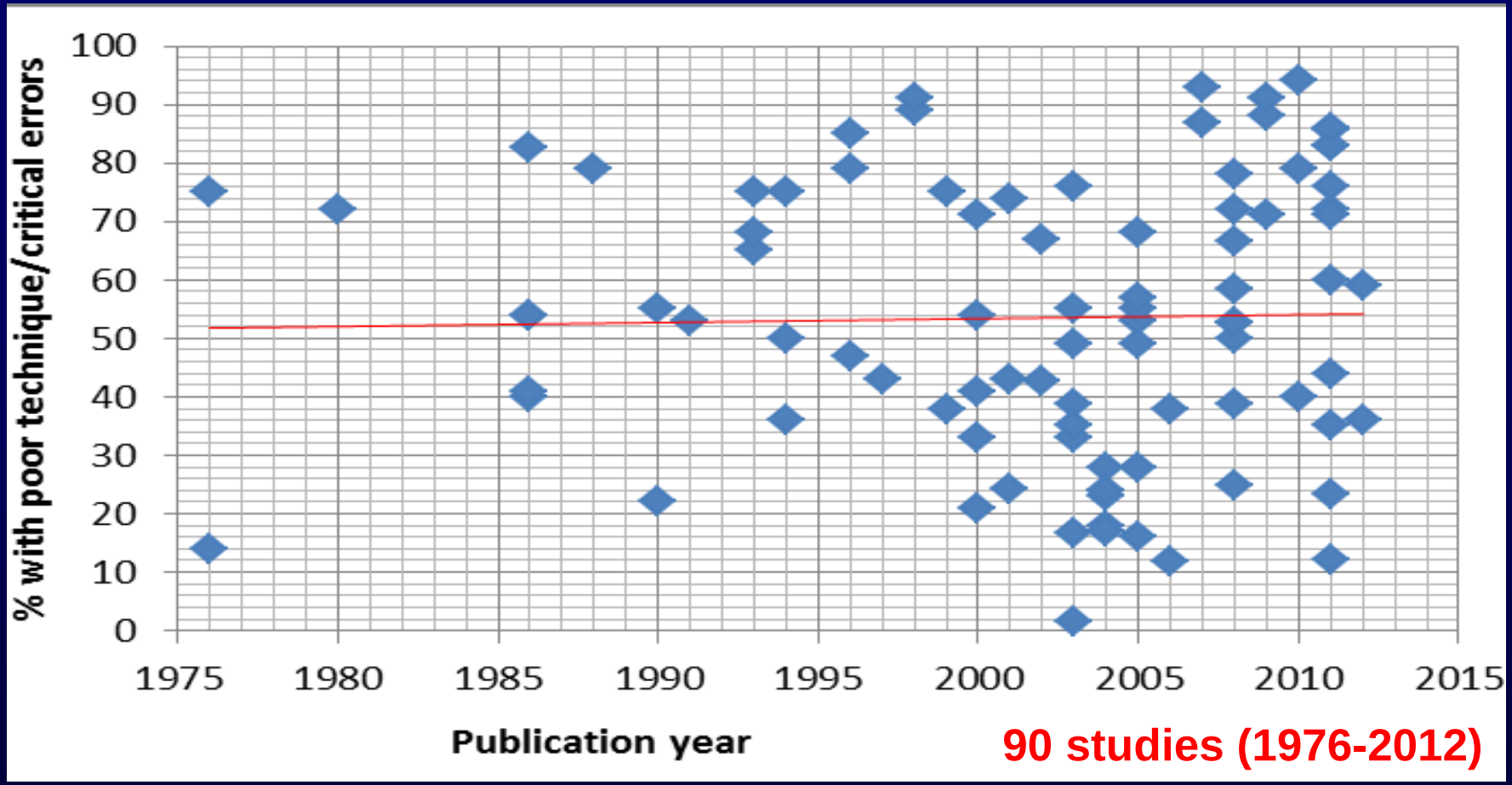
HFA-driven pMDIs & Technology Changes





Leach CL et al. Am J Respir Crit Care Med 2000

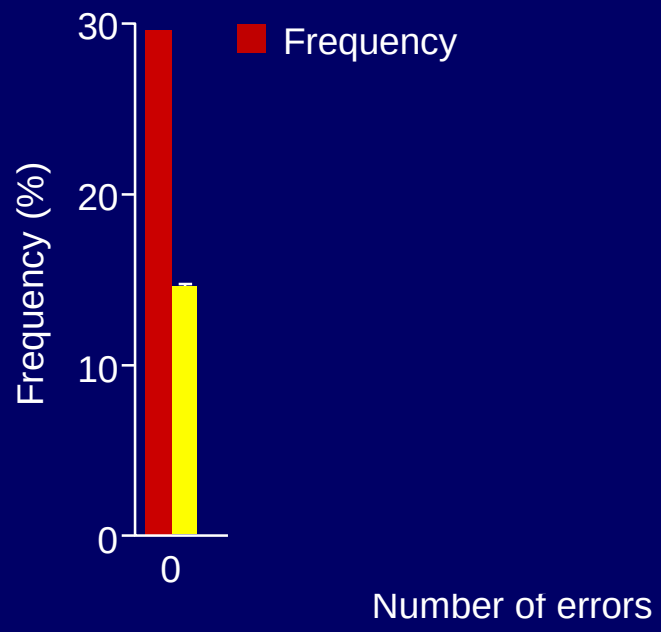
- ✓ Low velocity "soft" spray; long plume duration;
- ✓ Small droplet size and high lung deposition;
- ✓ Clinically effective at half the dose of traditional pMDI.



Despite the development of new inhalers = there has been no sustained improvement over the past 35 years in patients' ability to use inhalers

Courtesy F. Lavorini. Personal communication

Number of errors in asthma relates to a reduction in control



Frequency distribution of the number of errors or omissions in inhalation technique

Asthma instability score (AIS) data: mean ± SEM

Correlation between number of errors and AIS (linear regression analysis): r=0.3, $p < 0.0001$

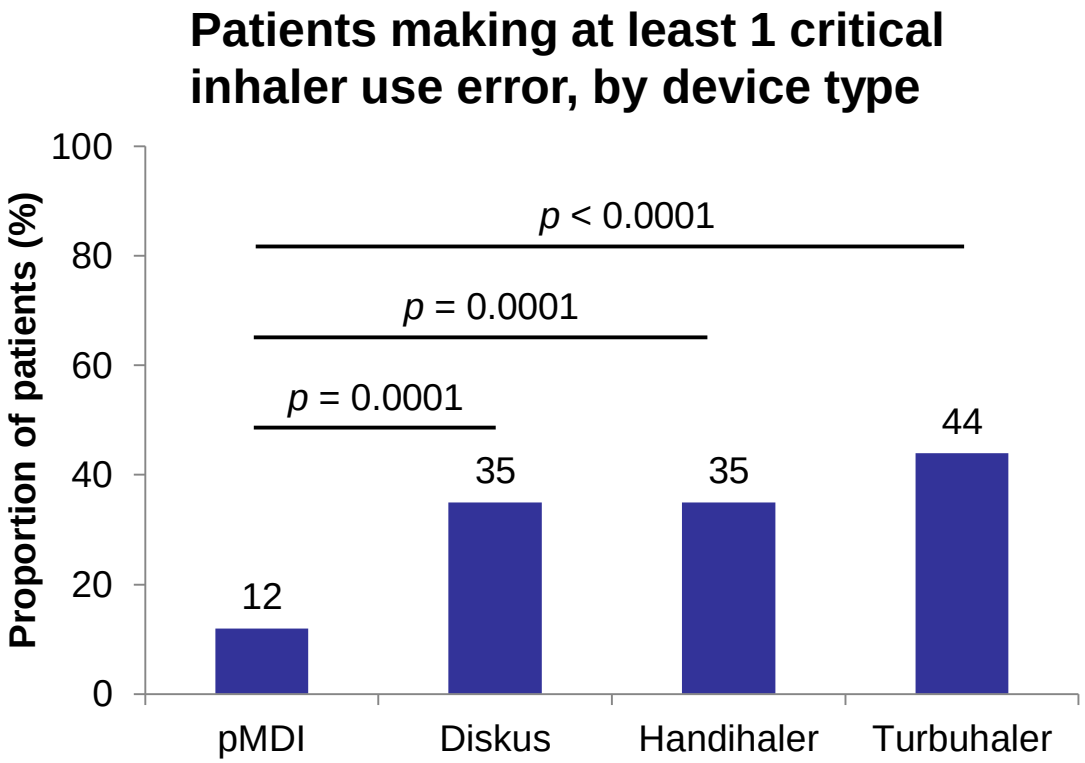
Giraud V, Roche N. *Eur Respir J* 2002;19:246–51

pMDIs were believed to be associated with more inhaler use errors than DPIs[1,2]

	Aerolizer (n = 769), %	Autohaler (n = 728) , %	Diskus (n = 894) , %	pMDI (n = 552) , %	Turbuhaler (n = 868) , %
At least one error	54 (50–57)	55* (52–59)	49 (46–53)	76* (73–80)	54* (51–58)
At least one device-dependent error	12 (10–14)	41* (38–50)	16* (14–19)	69* (66–73)	32* (29–35)
At least one critical error	12 (10–14)	11 (9–14)	11 (9–13)	28* (24–32)	32* (29–35)
GP's opinion (patient inhaled the right dose)	80 (77–83)	66* (62–69)	75* (72–77)	50* (46–54)	70* (67–73)
Overestimation by GP	11* (8–13)	6 (4–8)	9* (7–11)	6 (3–9)	24* (21–28)

*$p < 0.05$ compared with the best result adjusted by age and sex.
Table adapted from Molimard *et al.* 2003.; N = 3811 patients with asthma; data are mean % (IC 95%)
1. Molimard M *et al. J Aerosol Med* 2003;16:249–54; 2. Souza MLM *et al. J Bras Pneumol* 2009;35:824–31.

However, other studies have questioned this



Cross-sectional, observational study in 1664 adults with asthma, COPD or other respiratory diagnosis in Italy

Melani AS *et al. Respir Med* 2011; 105:930–8

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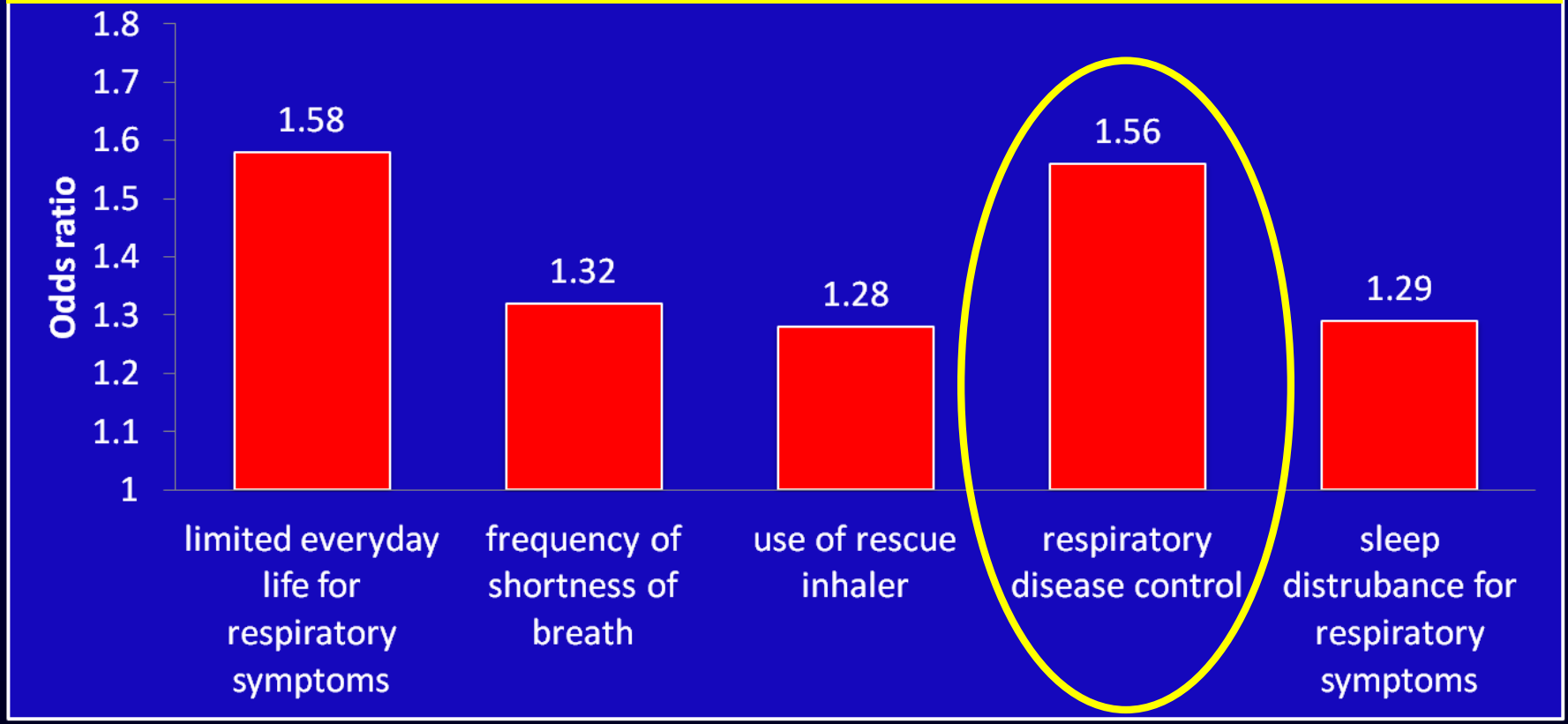
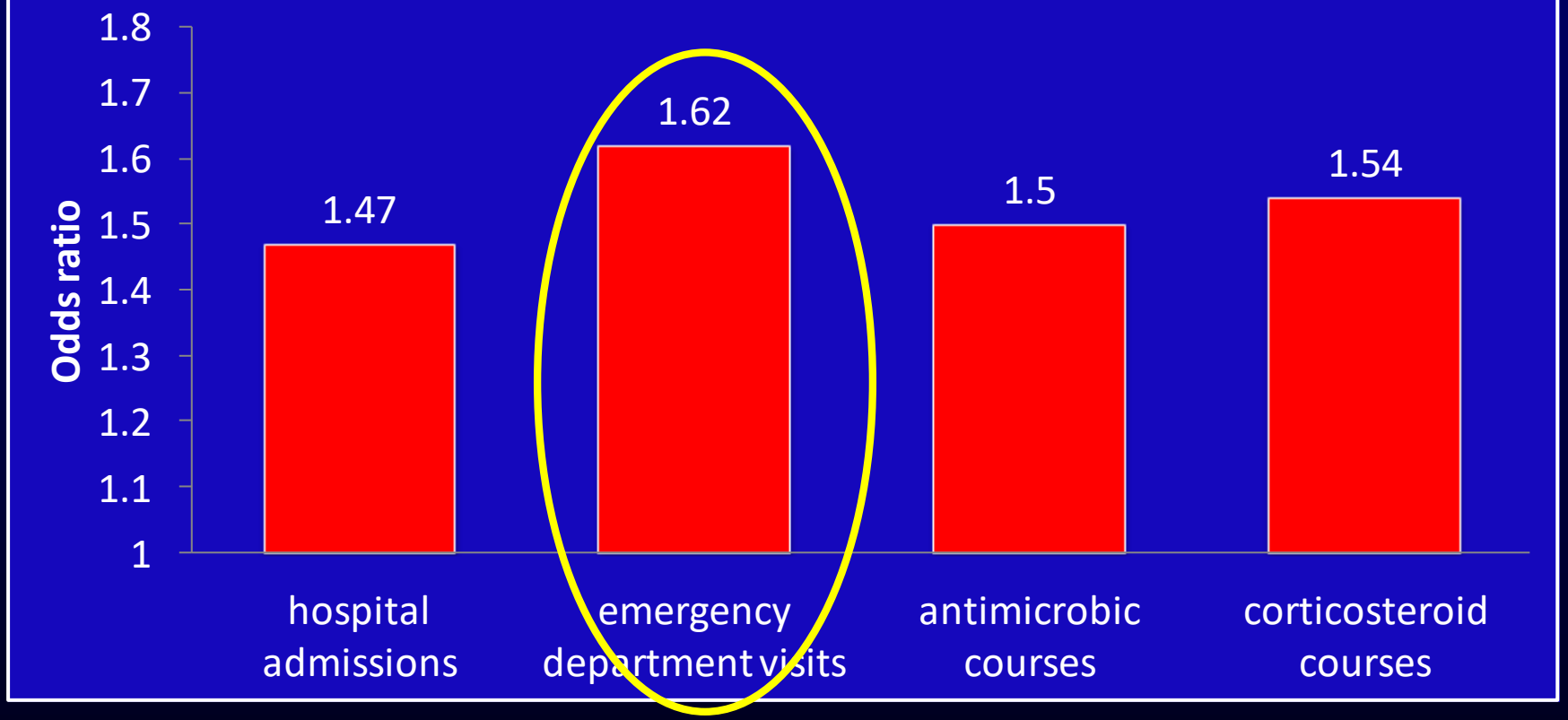
- **Disegno di uno studio**

Association between Disease Control and at least *one* Critical Inhaler Error



Melani, Gruppo Educazionale Associazione Italiana Pneumologi Ospedalieri Resp Med 2011

Association between Heath Care Resource Use and at least *one* Critical Inhaler Error

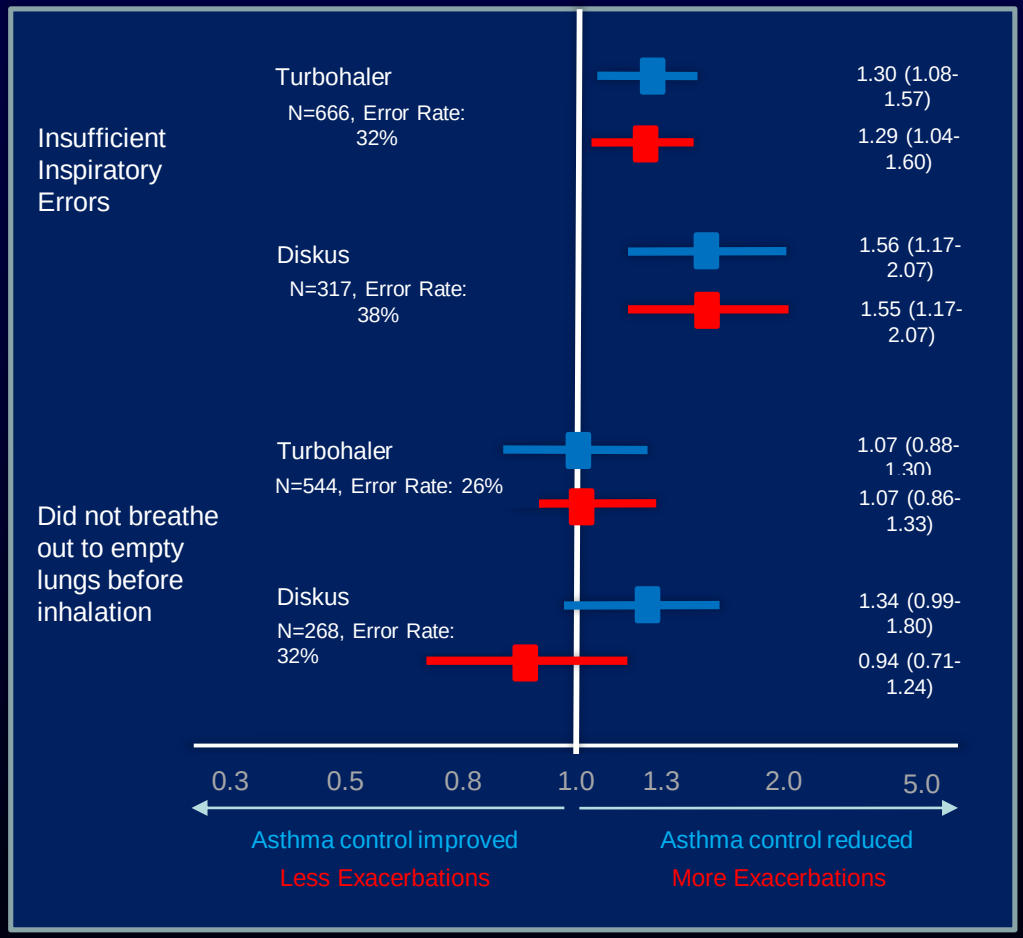


Melani, Gruppo Educazionale Associazione Italiana Pneumologi Ospedalieri Resp Med 2011

CRITIKAL: Insufficient Inspiratory Effort in DPI users had significant association with Uncontrolled Asthma and Exacerbation

The CRITIKAL study confirmed the importance of fast inhalation.

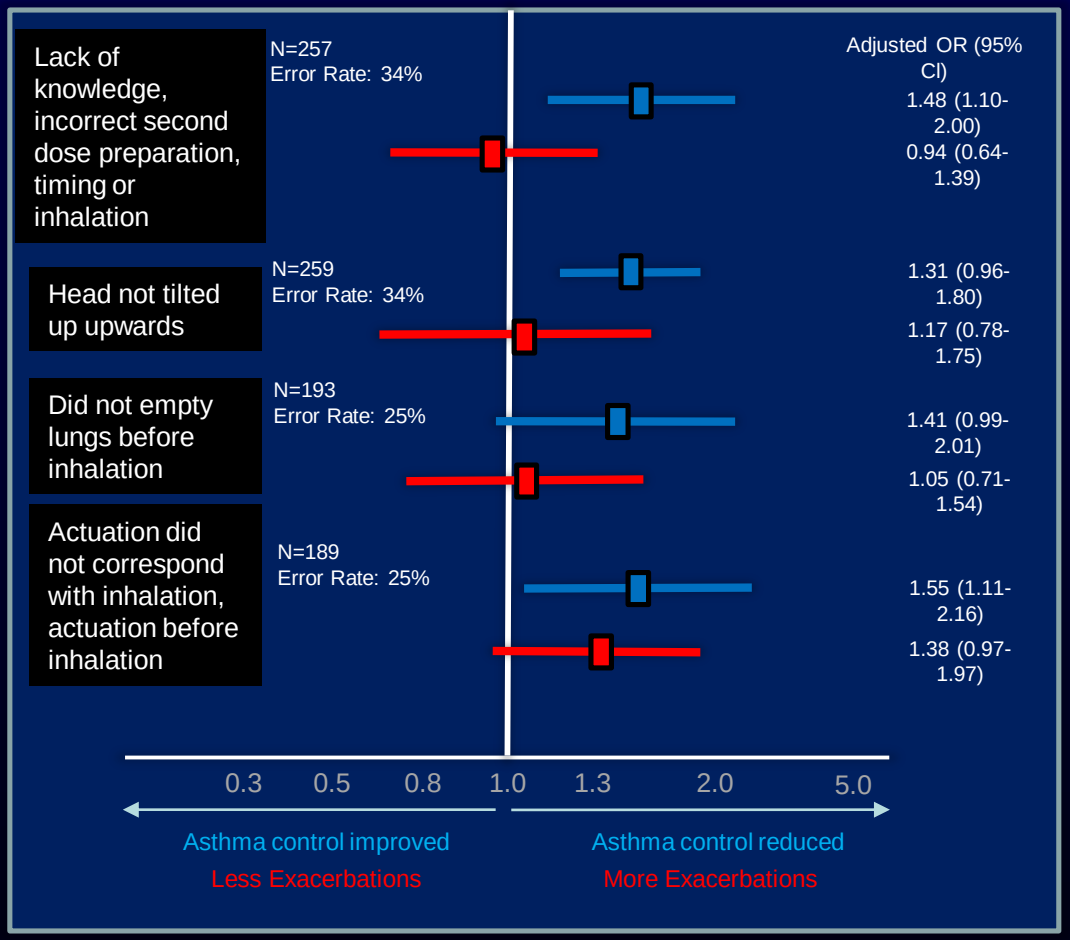
Insufficient inspiratory effort was significantly associated with an increased likelihood of being in the uncontrolled asthma category and was significantly associated with increased exacerbation rate among DPI users



Association between inhaler errors (for DPIs) uncontrolled asthma and exacerbation

Price D et al. March, 2017

CRITIKAL: MDI Errors were not significantly associated with Exacerbation rate



Association between inhaler errors (for DPIs) uncontrolled asthma and exacerbation

Actuation before inhalation was common (made by 24.9% of patients) and was associated with uncontrolled asthma after adjustment by patient factors

The most frequent error, “inspiratory effort not slow and deep,” was not associated with uncontrolled asthma.

After adjustment by patient factors, none of the MDI errors was significantly associated with exacerbation rate

Price D et al. March, 2017

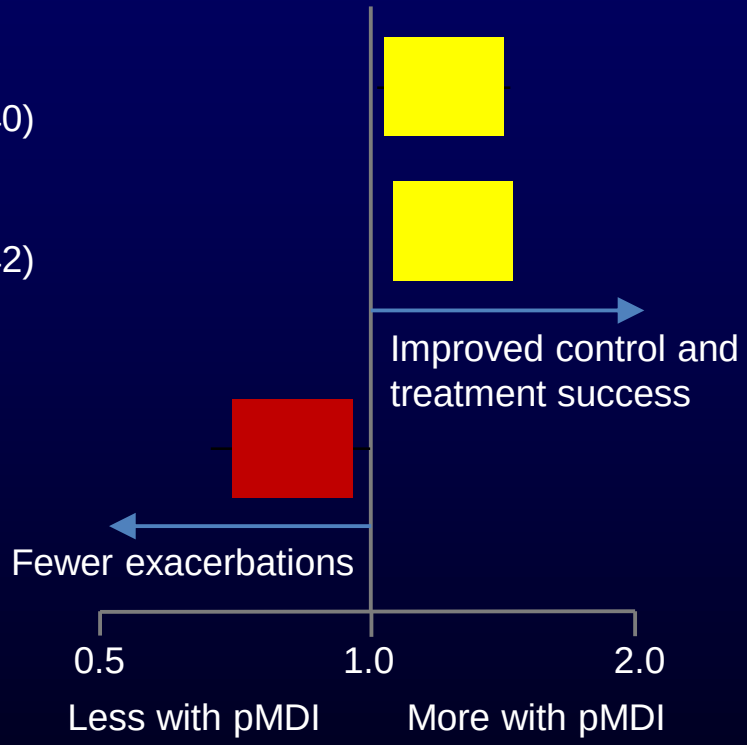
In the UK, pMDIs may improve asthma control versus DPIs for the administration of ICS/LABAs

Comparison of FP/SAL pMDI with FP/SAL DPI[a]

Primary measure of asthma control
Unadjusted OR: 1.19 (95% CI: 1.01, 1.40)

Treatment success
Unadjusted OR: 1.23 (95% CI: 1.07, 1.42)

Exacerbations
Adjusted RR: 0.82 (95% CI: 0.66, 1.00)



[a]For FP/SAL pMDI (Evohaler®) vs DPI (Accuhaler®). A retrospective, 2-year (1 baseline year, 1 outcome year), matched-cohort study using data from 3134 patients from the UK General Practice Research Database. Data are shown for end of outcome year for patients initiating fixed-dose therapy. Asthma control was a composite measure comprising no recorded hospital attendance for asthma, oral corticosteroids, or antibiotics for lower respiratory infection. Treatment success was defined as no exacerbations and no change in asthma therapy
Figure adapted from Price D *et al. Respir Med* 2011;105:1457–66

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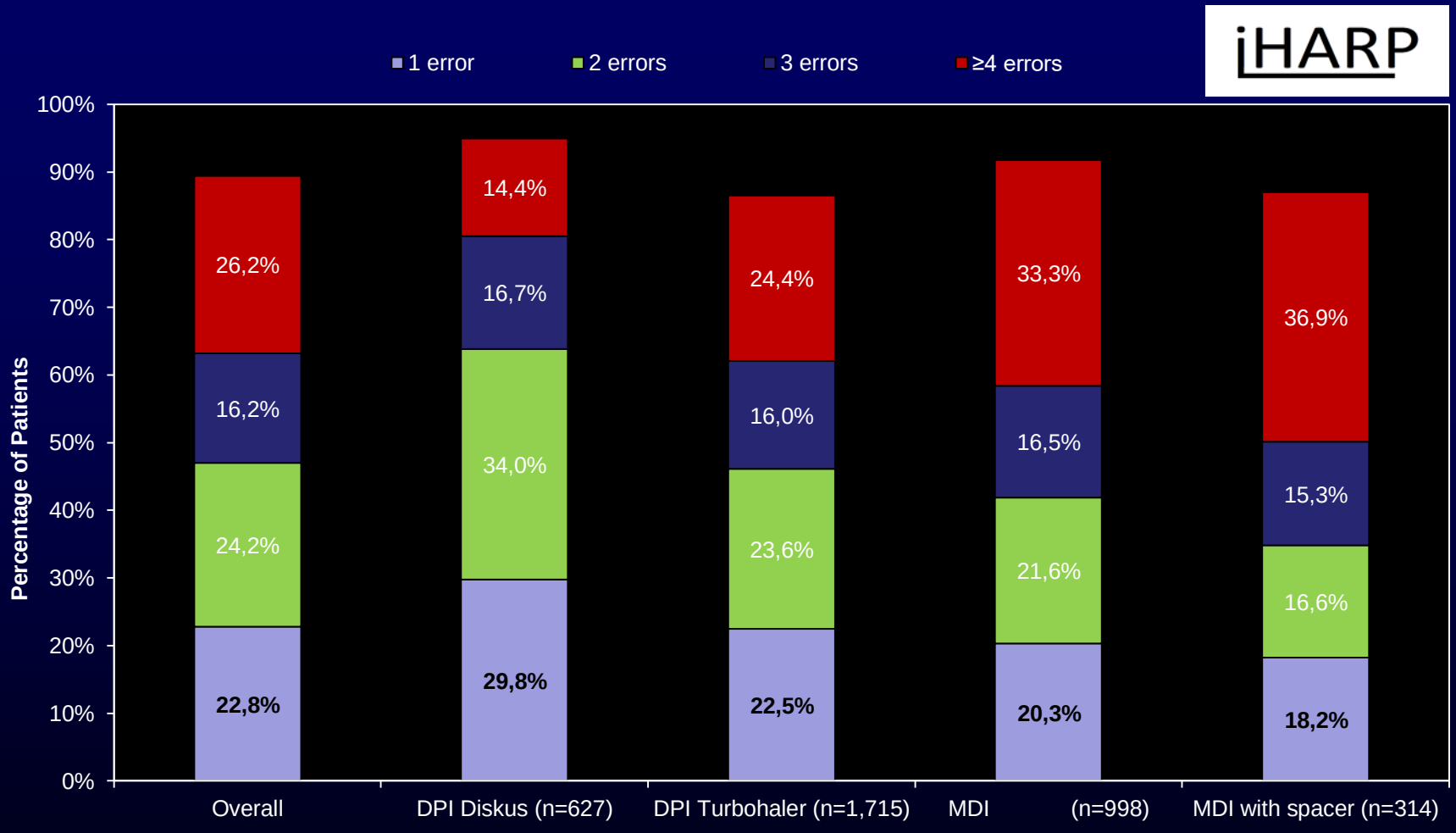
- **Disegno di uno studio**

More than 90% Patients make ≥1 potentially serious inhaler error



Price D, et al. 2014 Abstract presented IPCRG 2014

Device selection and outcomes of aerosol therapy: evidence-based giudelines ACCP/ACAAI.

Dolovich MB et al, Chest 2005

- ✓ *Aims*: Compare efficacy of pMDIs (+/- spacers), DPIs and nebulisers as delivery systems for β_2-agonists and corticosteroids in several clinical settings (ER, chronic, ITU) and different patient populations
- ✓ *Results*: none of the pooled meta-analyses showed significant differences between devices in any efficacy outcome OR patient group.
- ✓ *Conclusions*: The relative effectiveness of inhalers does ***not*** provide a clear basis for selecting one device over another.

= Choice of inhaler does not matter if patients use inhalers properly

What do Patients Want?

Device factors

- Perceived device efficacy
- Easy of use of device
  - Need for actuation/inhalation coordination
  - Ability to actuate device (strenght, arthritis issues)
  - Ability to generate sufficient inspiratory flows (DPI)
- Convenience of device
  - Dose and refill frequency
  - Dose counter
  - Availability of combination inhalers
- Feelings of stigmatization due to need for device use in public
- Physician device prederence
- Availability of drug/device preparations
- Brand loyalty
- Cost
- Time to learn: clear instructions
- Size, weight, taste, device appearence
- Cleaning issues
- Disposability/environmental isseues

Hodder, Int J COPD 2009

Inhalers
What do Physicians Want?

Main criteria driving physicians' choice of an inhaler:

- ease of use
- no need for coordination
- low inspiratory flow required for inhalation
- perception of drug intake
- presence of a dose counter

→ **Feedback**

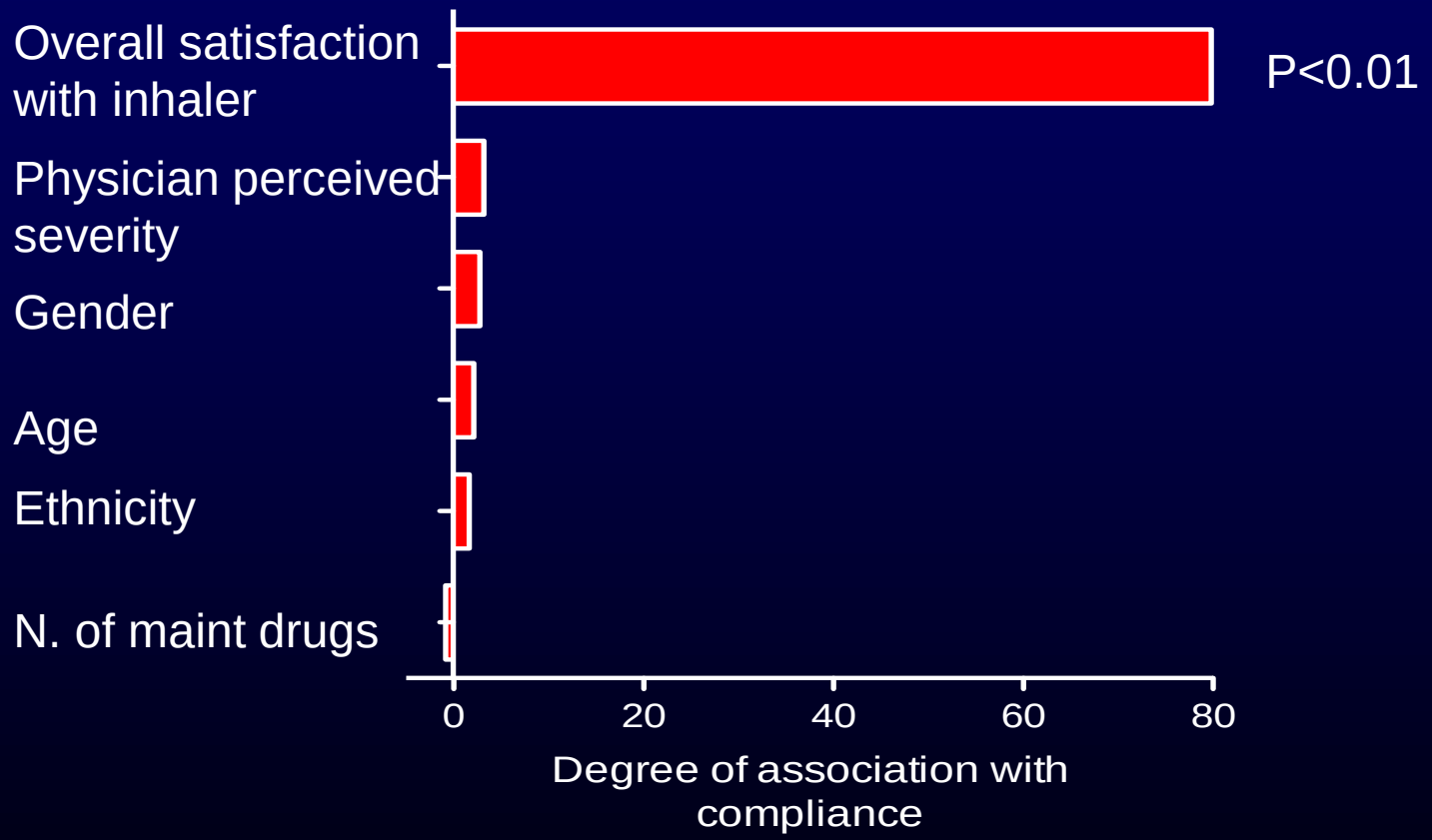
Physicians believe available inhalers can be improved by:

- reducing the possibility of making errors during inhalation
- reducing the time for teaching (physicians) and understanding (patients) how to use the device
- consistent dose delivery to effectively relieve patient's symptoms
- increasing the patient's confidence in dose intake

EU Market International Research 2011 (Kantar Health)

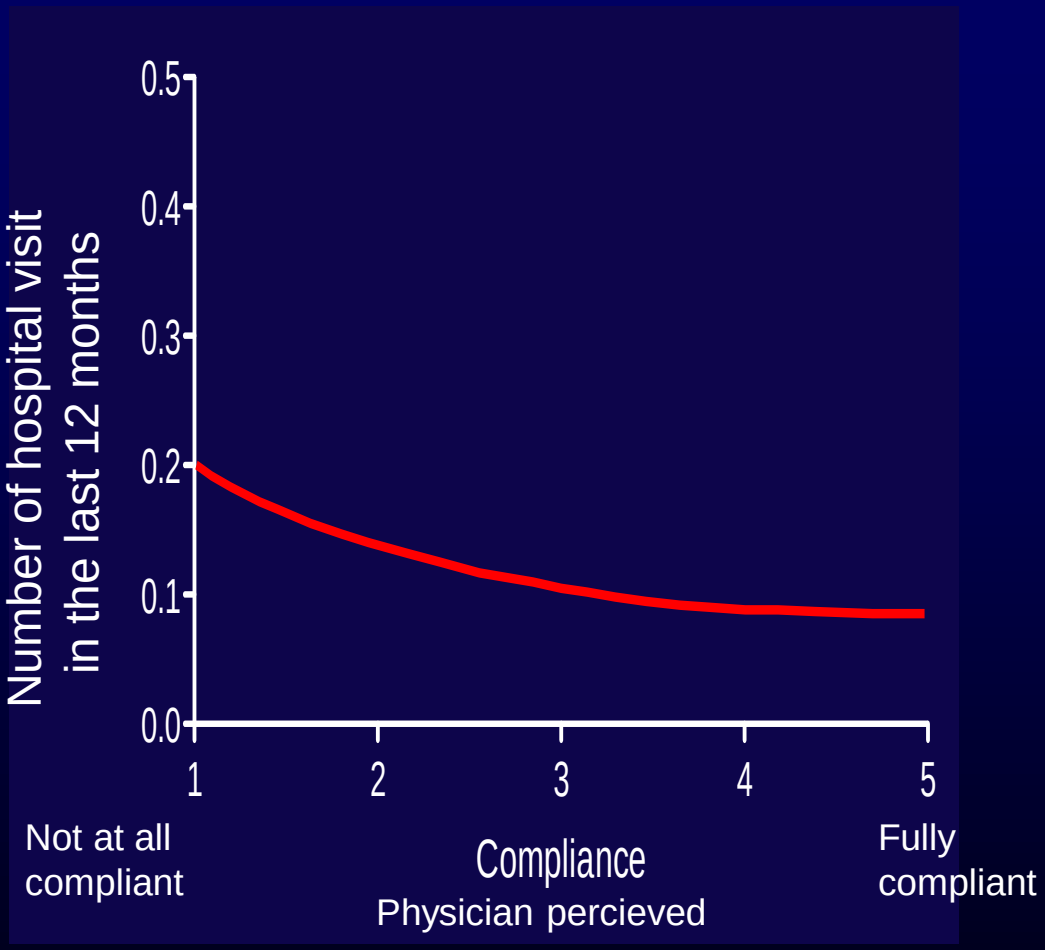
Patient Satisfaction with inhalers

- A significant correlation has been shown between patient satisfaction with their inhaler and adherence to treatment.



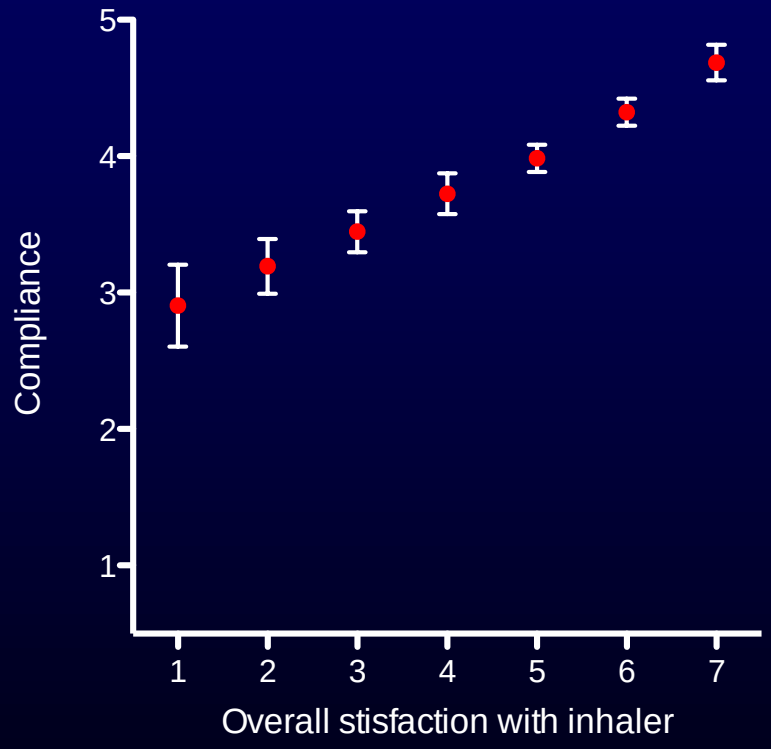
Small M et al, Adv Ther 2011

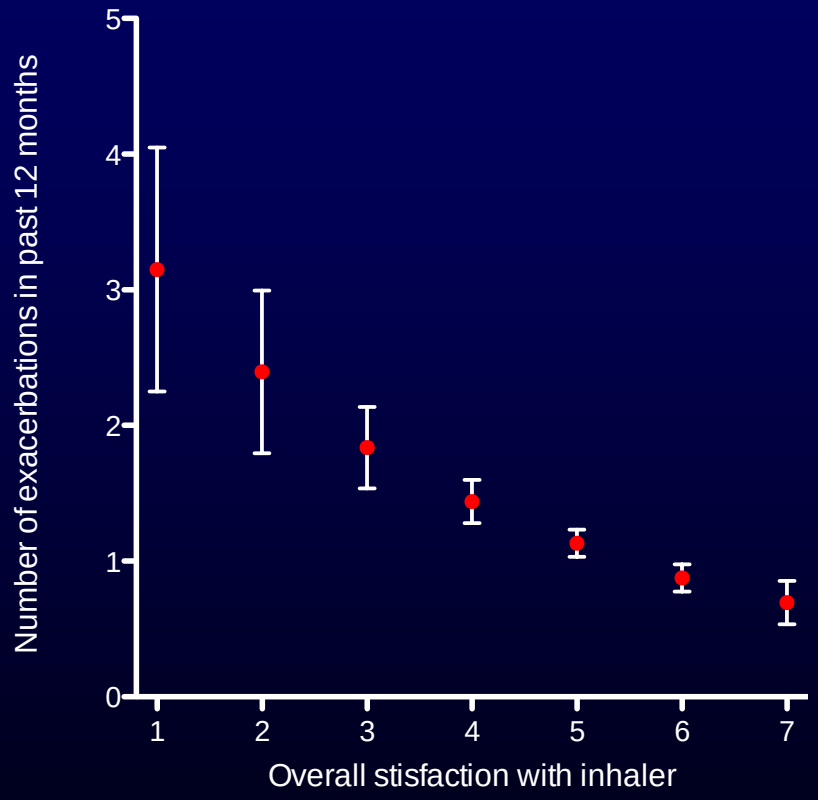
Patient Satisfaction with inhalers



Small M et al Adv Ther 2011

Impact of patients' satisfaction with their inhalers on treatment compliance and health status in COPD





(*Chrystyn et al. Respir Med 2013)*

PASAPQ*

	Domain		Question	Description
Part I	Total score	Performance	Q1	Overall feeling of inhaling
			Q2	Inhaled dose goes to lungs
			Q3	Amount of medication left
			Q4	Works reliably
			Q5	Ease of inhaling a dose
			Q10	Using the inhaler
			Q11	Speed medicine comes out
		Convenience	Q6	Instructions for use
			Q7	Size of inhaler
			Q8	Durability of inhaler
			Q9	Ease of cleaning inhaler
			Q12	Ease of holding during use
			Q13	Convenience of carrying
	Standalone		Q14	Overall satisfaction
Part II			*	Preference
			*	Willingness to continue

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- **Disegno di uno studio**

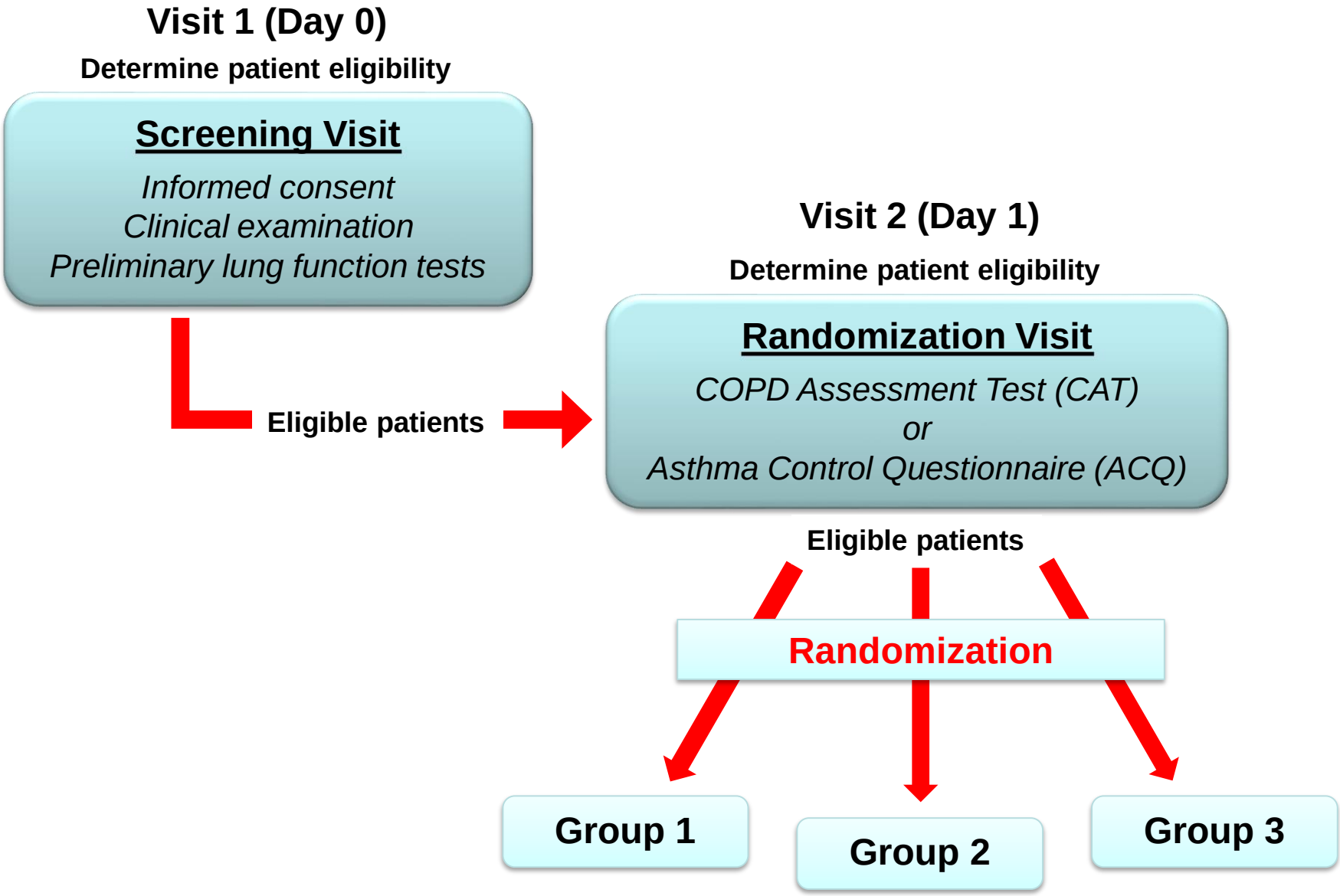
Overview

- Clinical Phase 3
- Open label
- Randomized, multicenter, active controlled, repeated measures – three sequences-design study
- 2 Phases: cross over + longitudinal

- Population
  - Adults over 60 years of age
  - Documented history of persistent asthma or COPD
  - Presently require ICS/LABA combination maintenance treatment
  - Sample size: 85 patients.

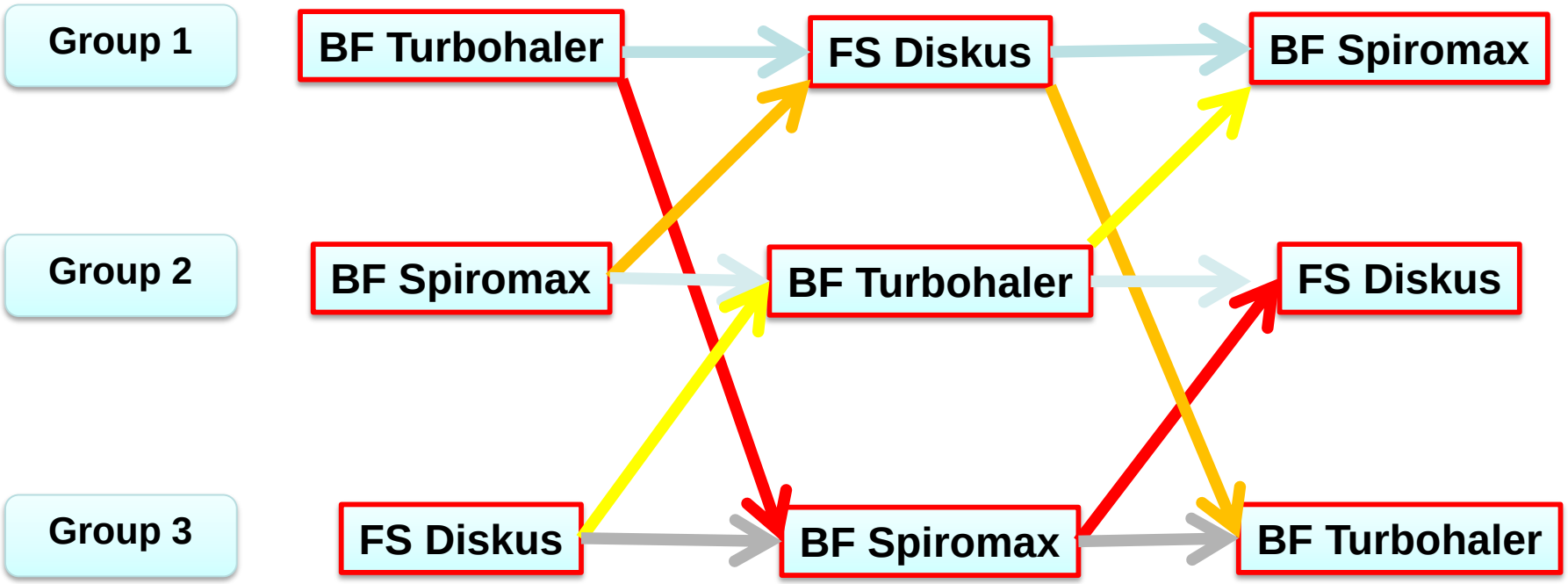
ICS/LABA = inhaled corticosteroid/long-acting beta$_2$-agonist

Screening and Randomization



Crossover Phase

Training Visit 2 (day 1) Treatment Days 1 – 7 Evaluation Visit 3 (day 8)	Training Visit 3 (day 8) Treatment Days 8 – 14 Evaluation Visit 4 (day 15)	Training Visit 4 (day 15) Treatment Days 15 – 21 Evaluation Visit 5 (day 22)



BF = budesonide and formoterol fumarate dihydrate; FS = salmeterol and fluticason propionate

Longitudinal Phase

Treatment
Days 22 – 78
Evaluation
Visit 6 (day 78)

Group 1	**BF Spiromax**
Group 2	**FS Diskus**
Group 3	**BF Turbohaler**

BF = budesonide and formoterol fumarate dihydrate; FS = salmeterol and fluticason propionate

Outcome Measures

- Primary Endpoint – Superiority - Device usability, expressed as total number of repeated attempts required to achieve optimal use during initial training (cross sectional phase).

ICS/LABA = inhaled corticosteroid/long-acting beta$_2$-agonist

Outcome Measures (cont)

- Secondary Objectives and Endpoints
  - Evaluate ease of use
    - Number of steps required for initial patient training
  - Evaluate short term maintenance of and long term correct use
    - Number of errors (including critical errors) after 1 week and after 8 weeks
  - Evaluate patient's preference for different devices
    - VAS and PASAPQ questionnaires scores
  - Evaluate effects on lung functional testing: FEV1, FVC, FEV1/FVC
    - Change from baseline after 1 week and after 8 weeks
  - Evaluate clinical outcomes
    - Symptom scores and use of rescue medications over 1 week
    - Changes in SGRQ, ACQ or CAT from baseline after 8 weeks

PASAPQ = Patient Satisfaction and Preference Questionnaire; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; SGRQ = St. George's Respiratory Questionnaire; ACQ = Asthma Control Questionnaire; CAT = COPD Assessment Test

Visit 2: RANDOMIZATION VISIT:
Clinical examination, lung function testing, CAT or ACQ questionnaires administered.
Patients will be trained regarding the use of a first inhaler device according to the following sequence:
1) Quick learning Visual. The pictures/figures/cartoons describing the correct use of the device, as reported in specific information leaflet, will be shown to the patients. Patients will be then asked to use the device as illustrated. Errors (if any) will be assessed according to a check lists obtained from the device instructions reported in information leaflet. If correct use (zero errors) is not attain the patients will enter the Reading phase.
2) *Quick learning* Reading instructions. Patients will read the information leaflet regarding the correct use of the device and will be asked to use the device as described. Errors counted. If correct use (zero errors) is not attain the patients will enter the Teaching phase a.
3a) *Quick learning* Teaching part a. Patients will be trained by a physician or an expert nurse on the correct use of the tested device and will be asked to use the device as trained. Errors will be evaluated. If correct use (zero errors) is not attain the patients will enter Teaching phase b.
3b) *Quick learning* Teaching part b. Patients will be repeatedly shown/trained to the correct use of the device until they will use it properly (zero errors). Total number of efforts to obtain the correct use will be counted.

• Patients will then receive 1 week treatment with the ICS/LABA combination delivered by the device they have been trained according to GINA/GOLD guideline recommendations. Diary card explained

Visit 3 (1 week after Visit 2):
Clinical assessment, diary card review (respiratory symptoms and rescue use) and lung functional tests will be performed.
A) The correct use of the first device will be assessed and the number of errors will be counted.
B) The first device will be returned and a second device assigned.
Patients will be trained regarding the use of this second inhaler according to the training steps (visual, reading instructions, teaching) previously described.

Visit 5 (3 weeks after Visit 2).
Clinical assessment, diary card review (respiratory symptoms and rescue use) and lung functional tests will be performed.
Patients will be evaluated on the ability in using correctly the third device and the number of errors will be counted.
Patients will be re-trained to the correct use of the last device they were assigned until they will use it properly (zero errors).
Patients will then receive 8 weeks treatment with the same regular ICS/LABA (same device) used during the last (third) period of the crossover phase.

Visit 6 At visit 6 (11 weeks after Visit 2)
Clinical assessment, diary card review (respiratory symptoms and rescue use) and lung functional tests will be performed.
Patients will be evaluated on the ability in using correctly the inhaler device and the number of errors will be counted.
SGRQ and either CAT or ACQ questionnaires will be administered as appropriate.
The satisfaction for different devices will be assessed by means of VAS (1-10). The satisfaction and preference questionnaire PASAPQ will be also administered

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