Intro to ePRO – Part I

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Agenda

- Overview of the ePRO Consortium and modes of administration (~20min)
- Discuss trends with collecting clinical data electronically (~20min)
- Q&A (~15min)

Critical Path Institute (C-Path)

- Established in 2005 by the University of Arizona and the FDA's Center for Drug Evaluation and Research (CDER)
- Dedicated to implementing FDA's *Critical Path Initiative* - a strategy for transforming the way FDA-regulated products are developed, evaluated, manufactured, and used
- An independent, non-profit organization
- Provides a neutral, pre-competitive venue for collaboration aimed at accelerated development of safe and effective medical products

ePRO Consortium

The Critical Path Institute established the ePRO Consortium on April 1, 2011

Mission: To advance the quality, practicality, and acceptability of electronic data capture (EDC) methods used in clinical trials for PRO endpoint assessment

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Benefits of Collaboration

A coordinated approach to gathering evidence supporting the measurement equivalence of the various ePRO modes

Collective development of ePRO migration best practices

- Methodological guidance on ePRO implementation in clinical trials (e.g., mixing modes within a trial)
- Development of publicly available specification documents for migrating specific PRO instruments to available ePRO platforms

PRO Consortium

Formed in late 2008 by C-Path, in cooperation with the FDA's CDER and the pharma industry

- Membership
  - 27 members (pharmaceutical firms) in 2014
- Non-Voting Participants
  - Representatives of governmental agencies (FDA, EMA, NIH)
  - Clinical consultants, academic researchers, patients, and CROs partnering in the development and testing of PRO instruments

PRO Consortium: Goals

- Develop qualified, publicly available PRO instruments for use in the assessment of primary or secondary clinical trial endpoints
- Enable pre-competitive collaboration that includes FDA input and expertise
- Avoid development of multiple PRO instruments for the same purpose
- Share costs of developing new PRO instruments
- Facilitate FDA's review of medical products by standardizing PRO endpoints

PRO Consortium Working Groups

Objective: To produce and/or compile the necessary evidence to enable new or existing PRO instruments to be qualified by the FDA for use in clinical trials where PRO endpoints can be used to support product labeling claims.

- Asthma
- Cognition
- Depression
- Functional Dyspepsia
- Irritable Bowel Syndrome
- Rheumatoid Arthritis
- Non-Small Cell Lung Cancer

Clinical Outcome Assessment (COA)

Clinical outcome assessment (COAs)

- Patient-reported outcome assessments (PROs)
- Clinician-reported outcome assessments (ClinROs)
- Observer-reported outcome assessments (ObsROs)
- Performance outcome assessments (PerfOs)

A patient-reported outcome (PRO) is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.

A PRO instrument is used to measure ***treatment benefit*** or risk in medical product clinical trials.

The Problem with Patient Satisfaction

Not part of FDA regulatory authority

21 CFR 314.126—”purpose of conducting clinical investigations of a drug is to distinguish between the effect of a drug from other influences…”

Pharma cares a lot—FDA sees no implication for labeling, particularly when the goal is comparative

The Problem with Health-Related Quality-of-Life (HRQoL)

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Might reflect treatment benefit, but not useful in the absence of a measure of core symptoms

Problems in generating labeling claims

- Logically distal outcomes
- Unclear expectations about change across duration of trial

Often risky strategy, better left to exploratory outcomes

Modes of Administration

- **Paper**
  - Digital Pen
- **Screen-based** – use an app or web interface
  - Handheld
  - Tablet
  - Desktop and Laptop Computers
- **Telephone-based**
  - Interactive Voice Response (IVR)

Improvements in Data Collection

Advantages of ePRO instruments over paper-based instruments

- contain the paper tornado
- avoid manual data entry and database creation
- more accurate and complete data

Benefits that do not exist on paper

- seamless skip logic, real-time edit checks, calculations, and alarms

May increase participation of subjects from typically underrepresented groups, such as those of lower income or lower literacy

Benefits of Electronic Data Capture

Allows the potential for event-driven data collection

- Concatenated items
- Complex items

Adaptive design

- Immediate data availability for decisions
- Monitor compliance

Enables real time compliance monitoring

Permits PRO data integration to eCRF

Recent ePRO-based Labeling Claims

Jakafi® - Incyte Corporation (2011)

- Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 handheld diary

  Secondary endpoint – comparison of proportion of subjects with a 50% or greater reduction in total symptom score

Subsys® - insys Therapeutics, Inc. (2012)

- Visual Analogue Scale handheld diary

  Primary endpoint – mean sum of pain intensity differences at 30 minutes (after administration)

Linzess™ - Ironwood Pharmaceuticals & Forest Laboratories (2012)

- 11-point NRS of Abdominal Pain at its Worst - IVRS

  Co-primary endpoint – along with Complete Spontaneous Bowel Movements

Is there a downside to ePRO?

Disadvantages of ePRO instruments over paper-based instruments:

- High technical and training burden on site and/or monitoring staff
- Management of eSource rather than more familiar paper source
- Data integration may occur outside of the clinical data system
- Unable to offer a paper back-up when employing skip logic, adaptive algorithms, etc.

May selectively decrease participation by subjects from unidentified subsets

Considerations for ePRO Migrations

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Infrastructure for electronic data collection

- Cellular signals, internet connectivity

Language and translations

- Assume that translated text will take more space (i.e., more characters) than US English
- Certain formatting does not translate well (e.g., fonts, capitalization, and underlining)

Benefits that do not exist on paper

- seamless skip logic, real-time edit checks, calculations, and alarms

But wait, there's a catch

"When a PRO instrument is modified, sponsors generally should provide evidence to confirm the new instrument's adequacy."

- From the FDA's PRO Guidance (FDA 2009)

  Section F. Instrument Modification, pages 20-21

"Examples of changes that can alter the way that patients respond to the same set of questions include:

- Changing an instrument from paper to electronic format
- Changing the order of items, item wording, response options, or recall period or deleting portions of the questionnaire
- Changing the instructions or the placement of instructions within the PRO instrument"

Items of Concern on Paper

Please complete either 6 or 7 (not both)

6. Decreased Appetite:

0 There is no change in my usual appetite.

1 I eat somewhat less often or lesser amounts of food than usual.

2 I eat much less than usual and only with personal effort.

3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

- OR -

7. Increased Appetite:

0 There is no change in my usual appetite.

1 I feel a need to eat more frequently than usual.

2 I regularly eat more often and/or greater amounts of food than usual.

3 I feel driven to overeat both at mealtime and between meals.

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., Markowitz, J. C., Ninan, P.T., Kornstein, S., Manber, R., Thase, M. E., Kocsis, J. H., and Keller, M. B. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C), and Self-Report (QIDS-SR): A Psychometric Evaluation in Patients with Chronic Major Depression. Biological Psychiatry, 54:573-583.

Types of testing for ePRO adaptation

Conceptual equivalence

- Do the subjects understand and interpret the modified instrument the same as the original paper-based instrument?

Statistical equivalence

- Are the scores obtained from the modified instrument the same as those from the original?

Coons SJ, Gwaltney CJ, Hays RD, et al (2009). Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force Report. *Value Health* 12(4):419-429.

Equivalence Testing

Qualitatively assess conceptual equivalence

- Small scale (n=15) cognitive interviewing to ensure understanding and ePRO usability
- The paper and electronic questionnaire may be completed by the subject, and the variation in response explored with the subject
- Not aimed at assessing the content of the original measure

  Poor paper measure = Poor electronic measure

Equivalence Testing

Quantitatively assess whether the data produced among alternative modes of administration are equivalent

- Larger scale (n=60-120), repeated-measure design
  - Crossover design, comparing paper and electronic
  - Assess score agreement (e.g., mean differences, ICC)
- Only necessary when moderate levels of change have been made during the migration
- Assumes the validity of the measure remains intact

Problems with Equivalence Testing

Authors may have varying opinions on demonstrating agreement

Paper is an imperfect “gold standard”

- Poor paper measure = Poor electronic measure
- Some items may have content validity, but perform poorly or have a lot of statistical noise

ePRO Recommendations

- Use ePRO with the understanding that there will be circumstances where it may not be appropriate
- Keep subject burden in mind/streamline user interface
- Expectations must be set with sites & patients
- Quality documentation must complement ePRO
- Adequate training will lower resistance & anxiety for new users
- Monitor compliance actively & educate sites about associated responsibilities
- If the Sponsor team is new to ePRO, appropriate training will ensure all understand the process and associated expectations
- Apply the same rigor to ePRO that is applied to PRO

Where are we with Patient-Driven eData?

Valdo Arnera, MD – PHT Corporation

Patient eData Annual Adoption 2002-2013

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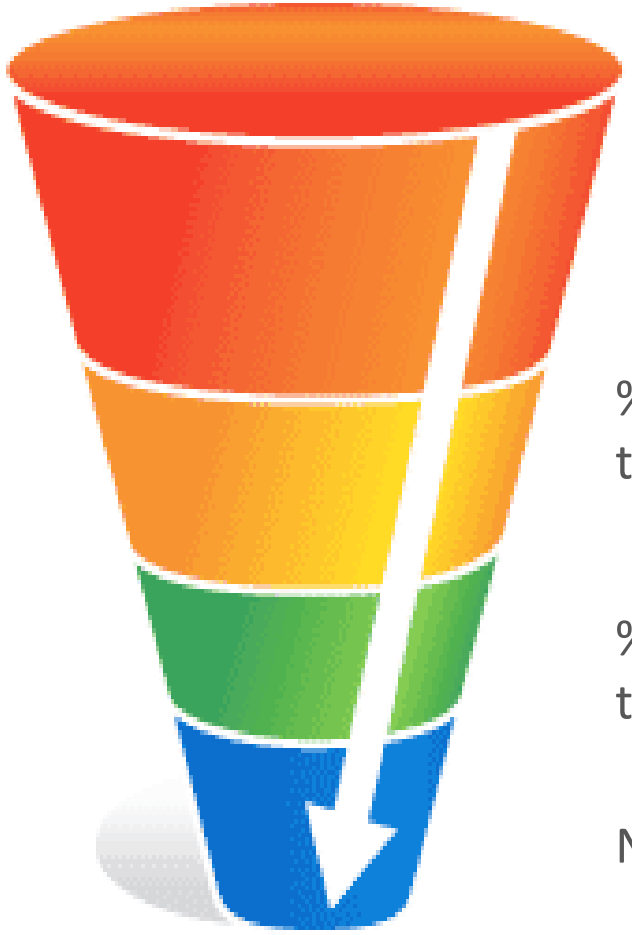
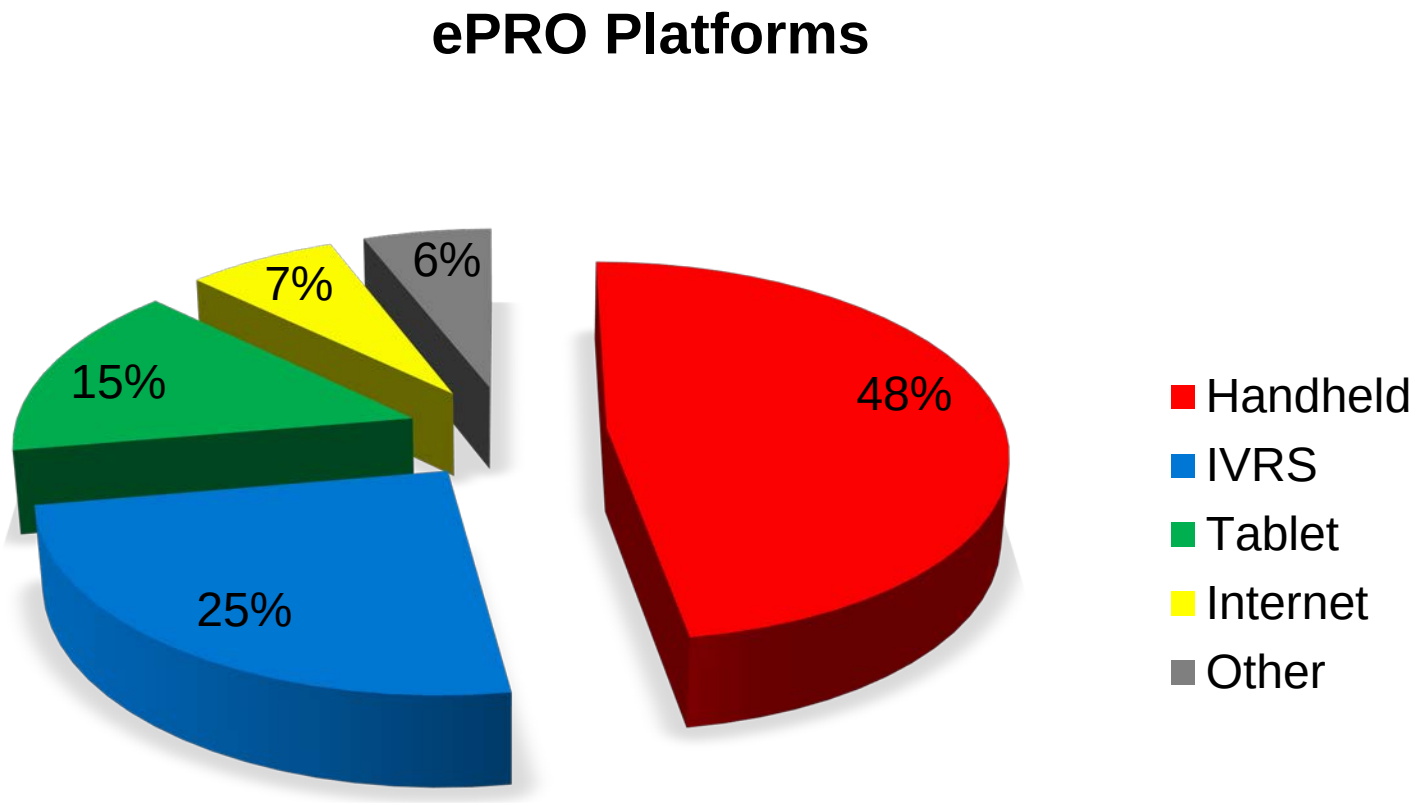


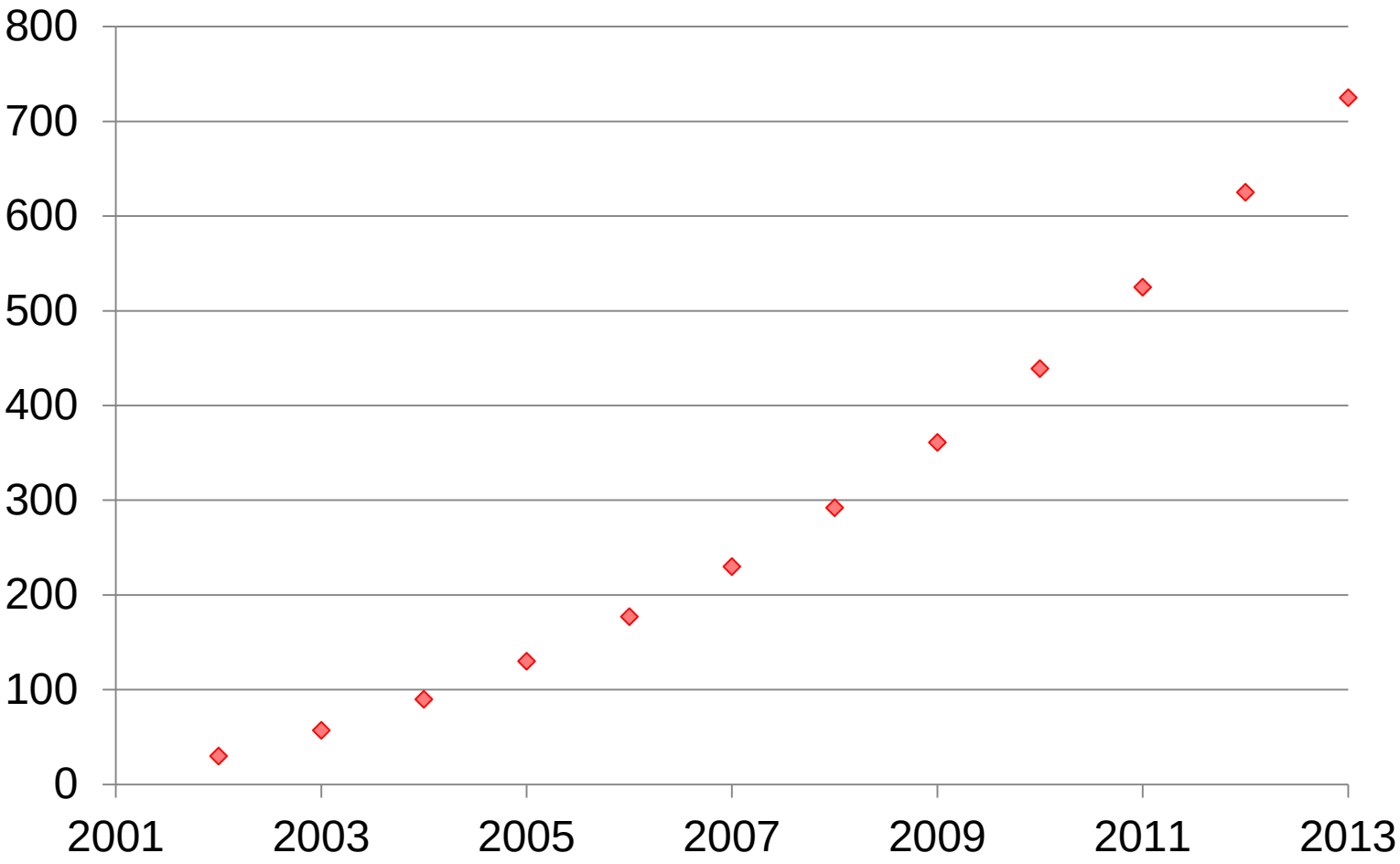
New trial starts	***4,000 → 5,250****
% of studies that Collect PRO Data	**15% → 35%***
% of studies that use ePRO	**5% → 45%***
Number of ePRO Trials	**30 → ?**

* PHT Corporation Estimates

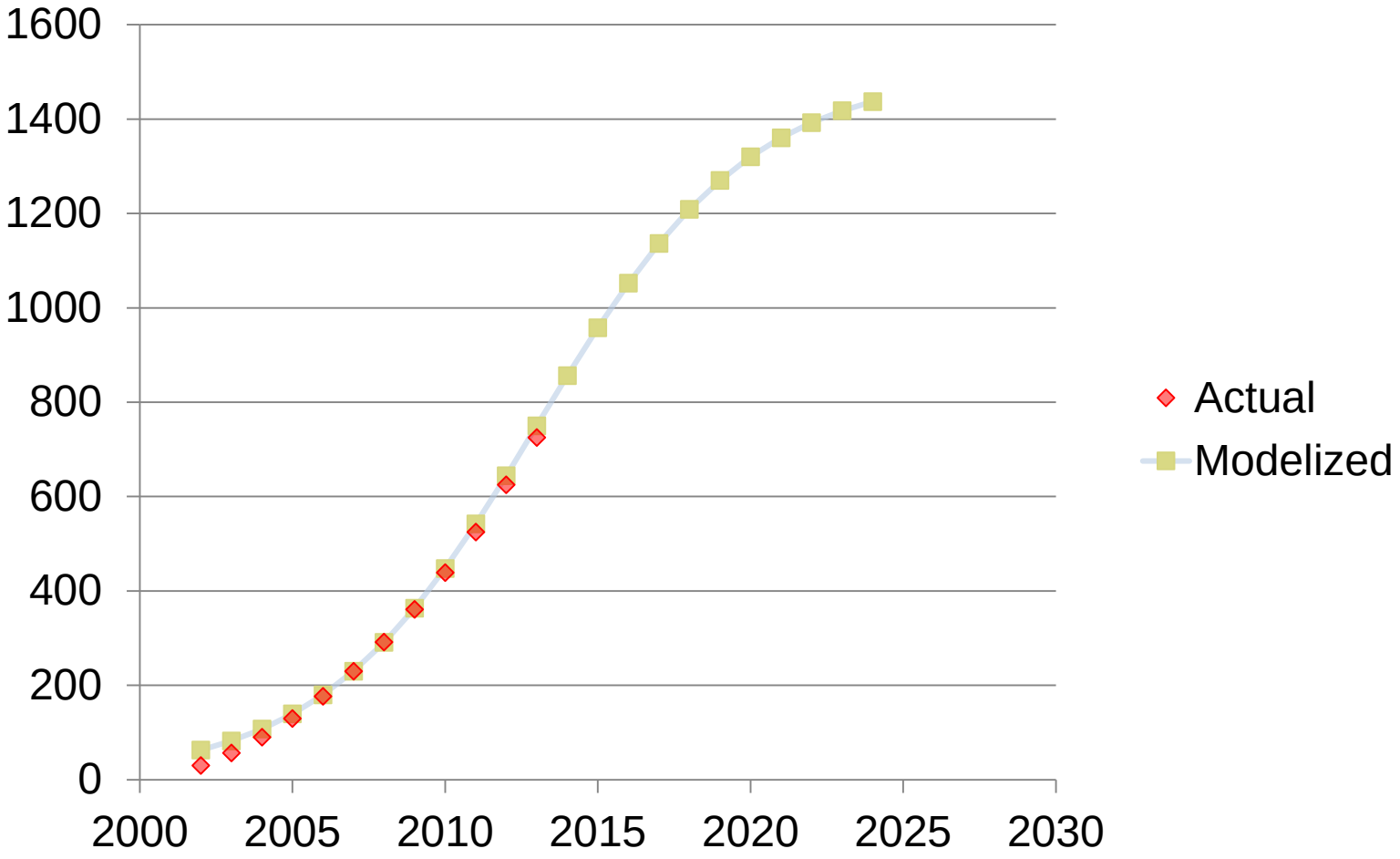
Patient eData Annual Adoption Rate - 2011



Number of Patient eData Trials 2002-2013



Number of Patient eData Trials 2002-2025 ?



Y=(1/(1+EXP(-1*0.284782*(X-2013)))*1500)

Increased Quality / Mode of Collection

- Insomnia
- Chronic Constipation
- Urinary Incontinence
- Asthma

The increased quality is very similar across TAs

Merck Insomnia Study

- One of the first randomized studies comparing eDiaries and paper on their relative capacity to show efficacy
- Two arms underwent an approved treatment for Insomnia
- Study performed by Merck Research Laboratories

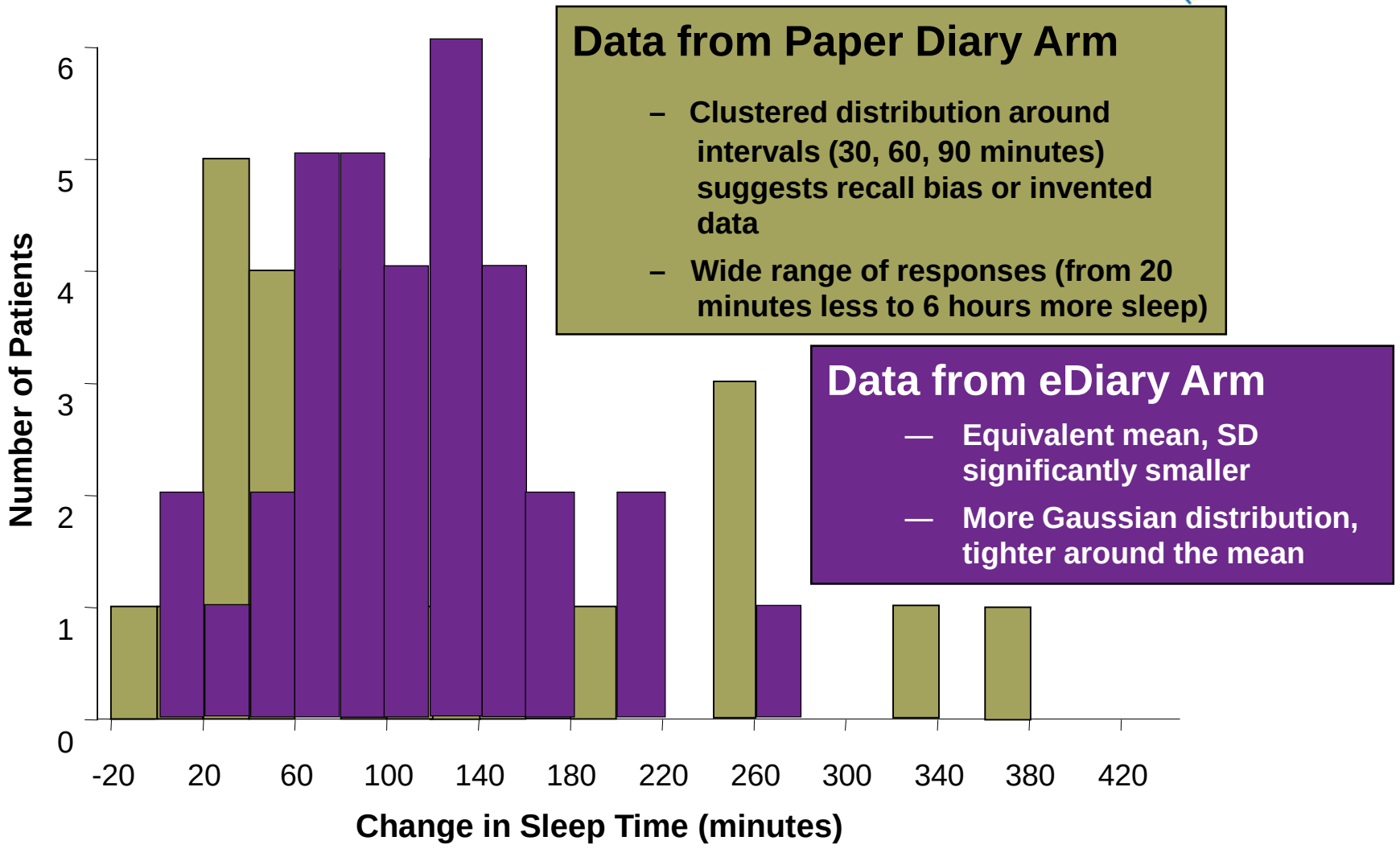
eDiary

Paper Diary Version

Answer questions 4-7 by entering a NUMBER (zero or greater) in each box.

7. How many hours did you sleep last night? _____ hours _____ minutes

Paper and eDiary Data: Δ Sleep Time



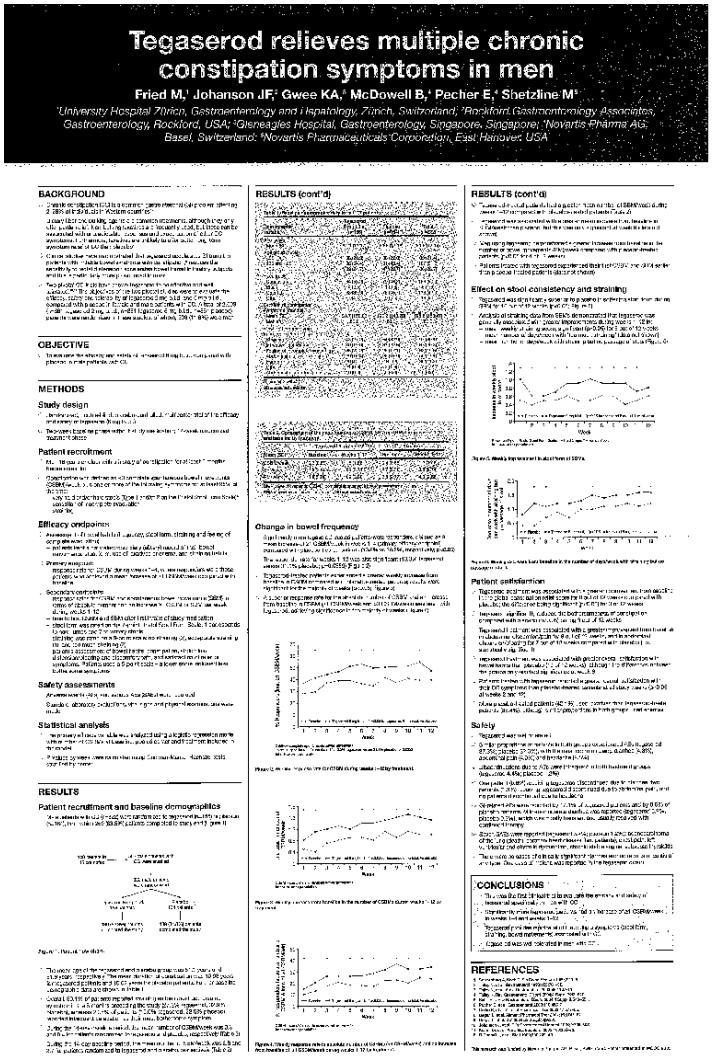
Summary of Results

Area of Interest in Trial	PHT LogPad	Paper Diaries
Calculated patients to yield 90% study power	**N=44**	N=101 (56% more than LogPad)
Potential cost savings	$340,000 *	--
Distribution of responses	**More Gaussian**	**Suggests recall bias**
Standard deviation	35% smaller	--
Sleep Change estimates	**Nearly identical**	--
Coefficient of variance	**Significantly smaller**	--
Data Point Changes and Notification Forms	--	**3x more of each**
Compliance (% of diaries completed)	**92%** objective **subject compliance**	**96%** purported **subject compliance**
Cost: **Data Entry (hr)** **Data Review (hr)**	**0** **10.5**	**58** **10.5**

* Estimated by assuming a total per-patient cost of $6,000

Results presented at DIA 2004 and at the International Society for Quality of Life Research (ISOQOL) 2004 symposium

Tegaserod in Chronic Constipation



Tegaserod relieves multiple chronic constipation symptoms in men

Fried M,[1] Johanson JF,[2] Gwee KA,[3] McDowell B,[4] Pecher E,[4] Shetzline M[5]

[1]University Hospital Zürich, Gastroenterology and Hepatology, Zürich, Switzerland; [2]Rockford Gastroenterology Associates, Gastroenterology, Rockford, USA; [3]Gleneagles Hospital, Gastroenterology, Singapore, Singapore; [4]Novartis Pharma AG, Basel, Switzerland; [5]Novartis Pharmaceuticals Corporation, East Hanover, USA

BACKGROUND

OBJECTIVE

METHODS

Study design

Patient recruitment

Efficacy endpoints

Safety assessments

Statistical analysis

RESULTS

Patient recruitment and baseline demographics

RESULTS (cont'd)

Change in bowel frequency

Effect on stool consistency and straining

Patient satisfaction

Safety

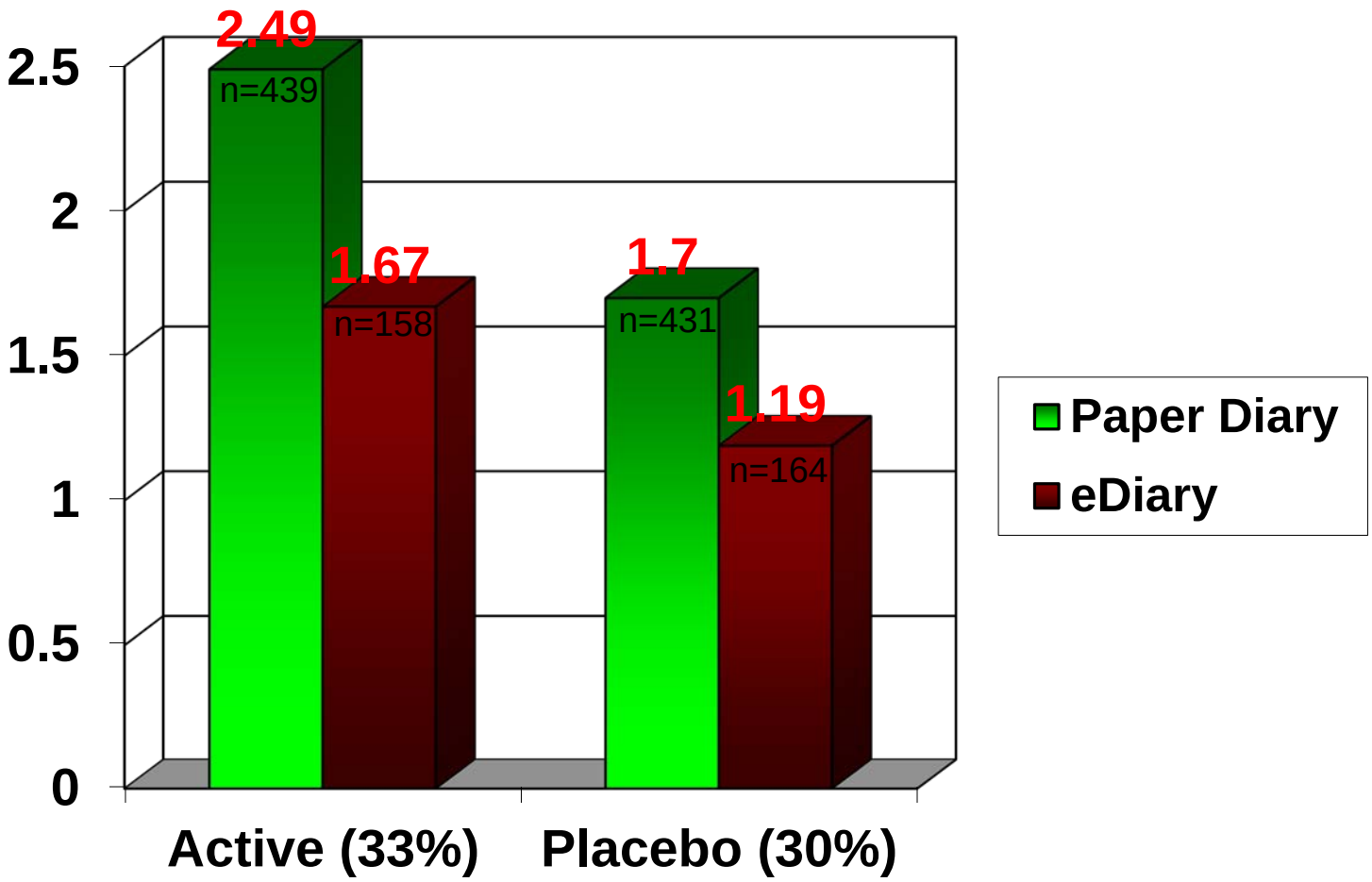
CONCLUSIONS

REFERENCES

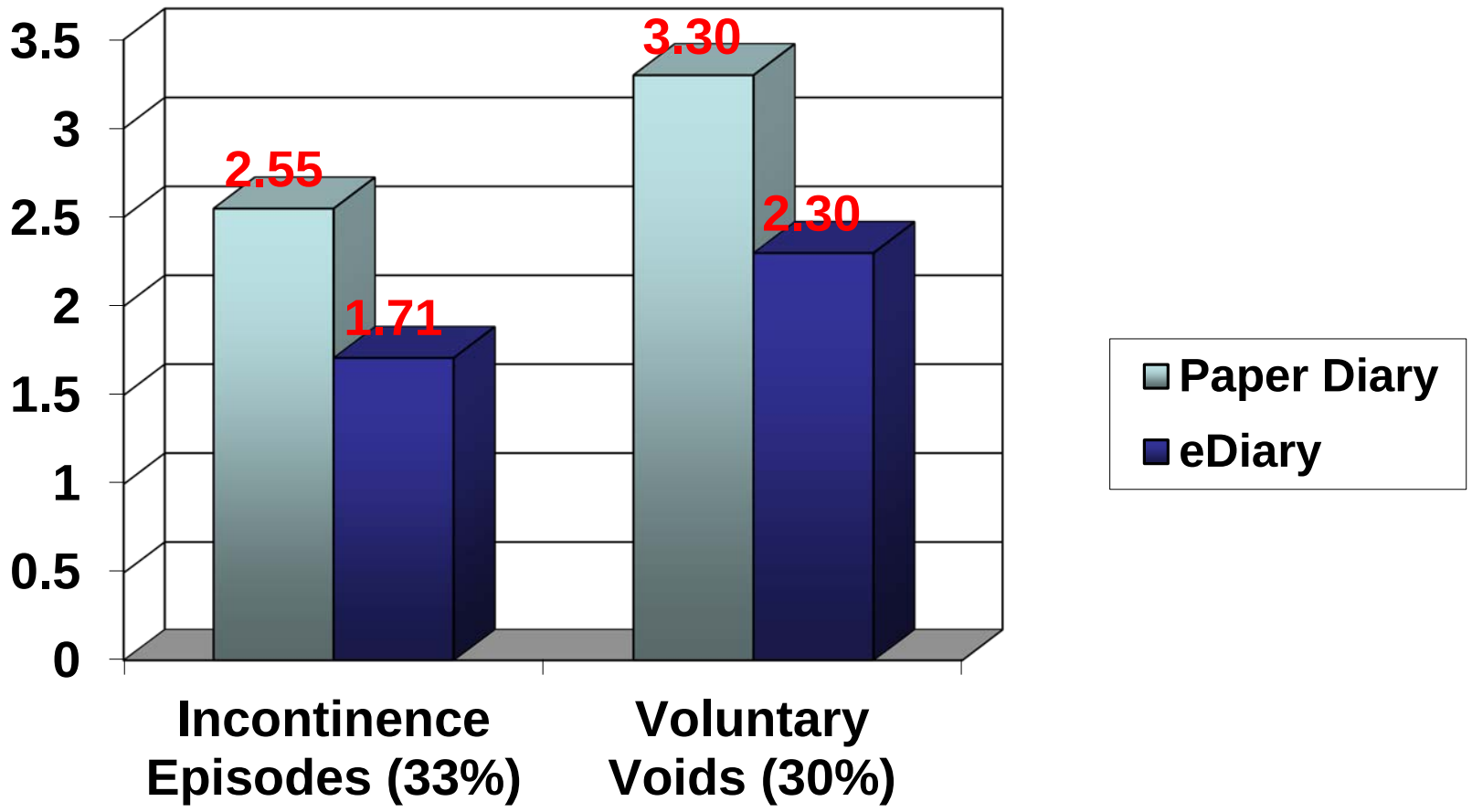
Poster presented at WCOG 2005

- Protocol had planned 1026 patients
- Study was interrupted
- Drug Efficacy was shown with 322 randomized patients

Differences in Std Deviation: Primary Efficacy Endpoint (CSBM)



Differences in Std Deviation: Primary Efficacy Endpoint (Micturitions)



S. McKenzie et al, "Proving the eDiary dividend", Applied Clinical Trials, Jun 2004

Increased Quality / Privacy

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A 4 weeks randomized cross-over trial to compare 2 methods of data collection (electronic and paper) in subjects with FSD

Female Sexual Encounter Profile (adapted)© Ferguson 2002

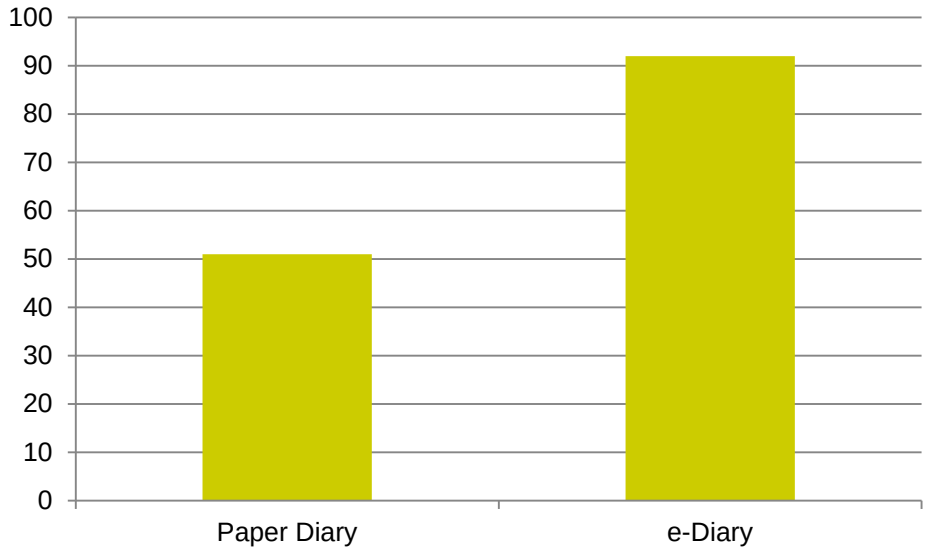
Inclusion Criteria

- Females with symptoms of sexual dysfunction
- In a stable, hetero-sexual relationship
- Minimum age of 18 yrs

Study included 27 Patients

One doesn't speak to paper the same way than to a PDA

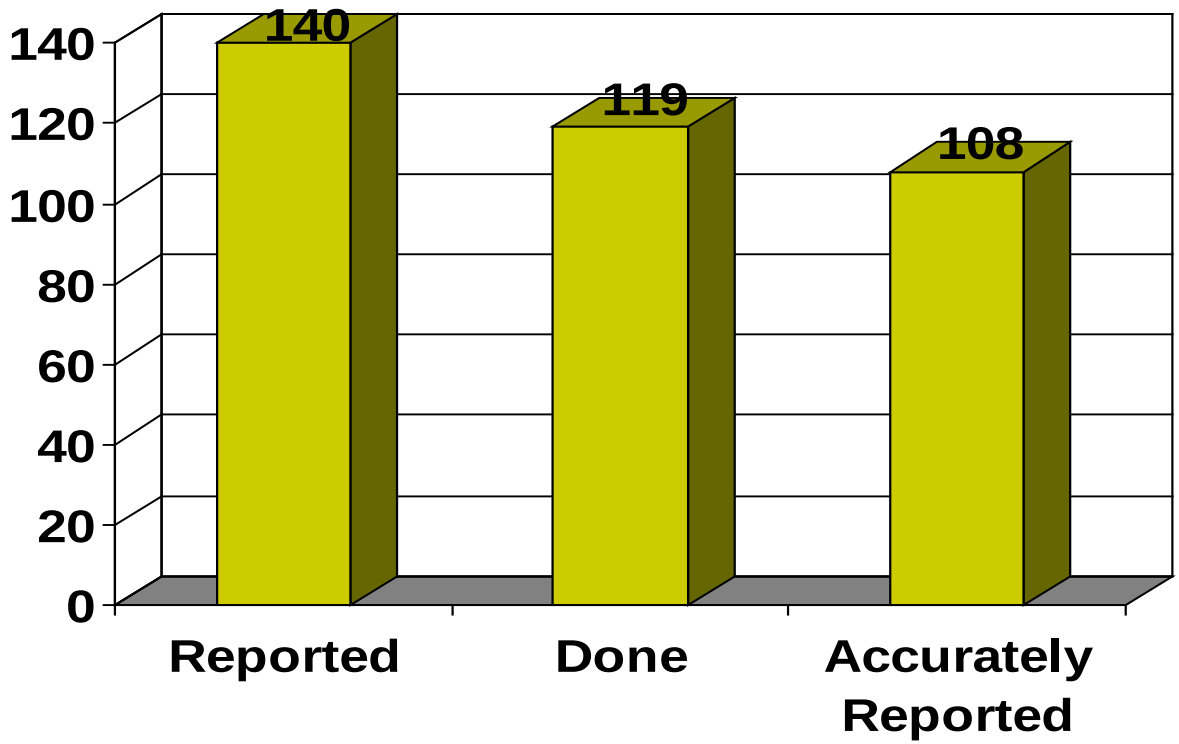
Increased Quality / Privacy



Female Sexual Encounter Profile Completion

Increased Quality / Cheating Prevention

Use of an electronic Peak Flow meter to assess compliance vs. paper diaries filled in by the patient.



Objective measurements of compliance in asthma treatment.
F. Chmelik et al, Annals of Allergy, Dec 1994

Increased Quality / Cheating Prevention

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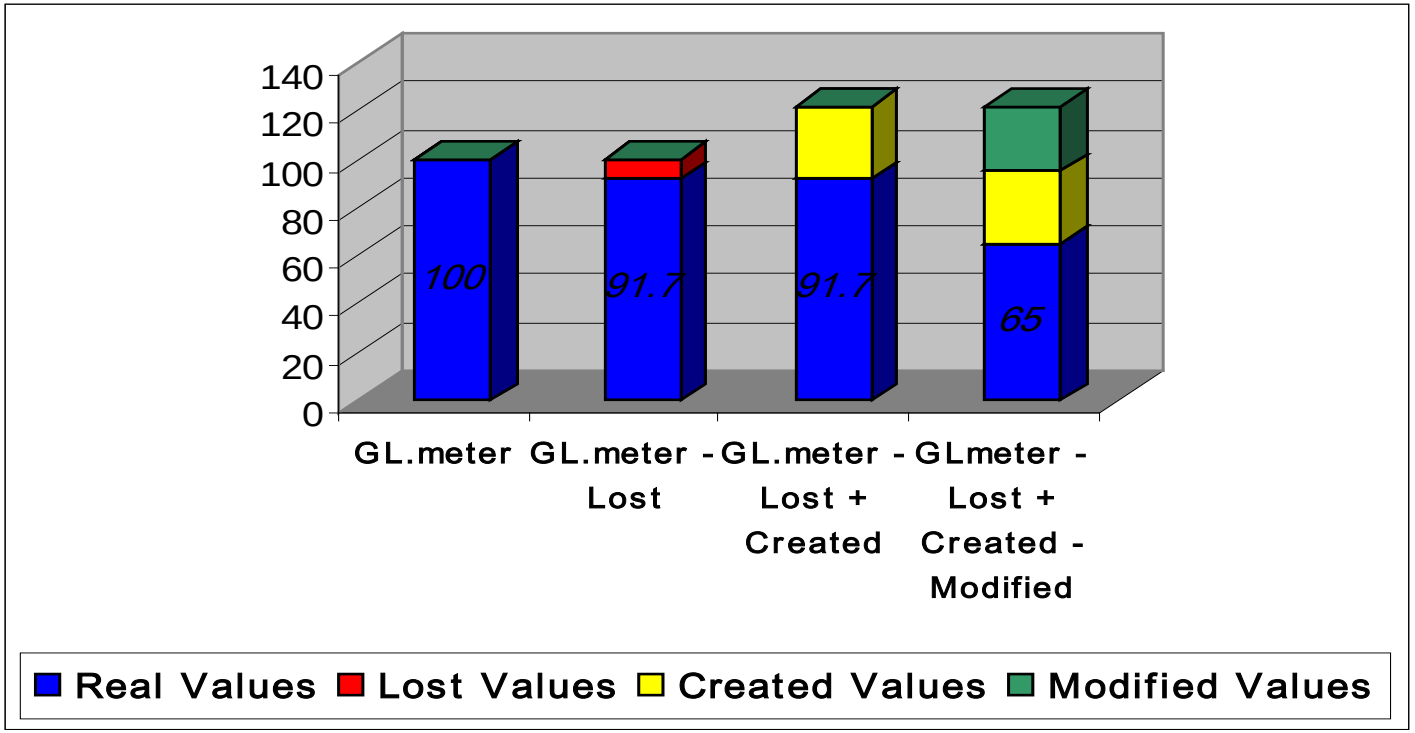
Blood Glucose Values recorded in the Glucometer and on the Paper diary



Reliability of Blood Glucose Monitoring by Patients with Diabetes Mellitus R.S. Mazze et al, The American Journal of Medicine, Aug 1984

Differences in SD: Efficacy Endpoint = PEF

New trial including 2300 patients, 6 months treatment

Approximately 90% paper diaries / 10% eDiaries

Aim: to investigate if the results differed between paper and eDiaries

Residual Standard deviation

	Morning PEF (L/min)
pDiary	44.1
eDiary	38.3

Use of an eDiary can decrease the variability in mPEF

Tendency of lower standard deviations in majority of eDiary endpoints

Indicate increase in the quality of the data

Increased precision → fewer patients needed

Integration of Objective Measurement Devices & ePRO

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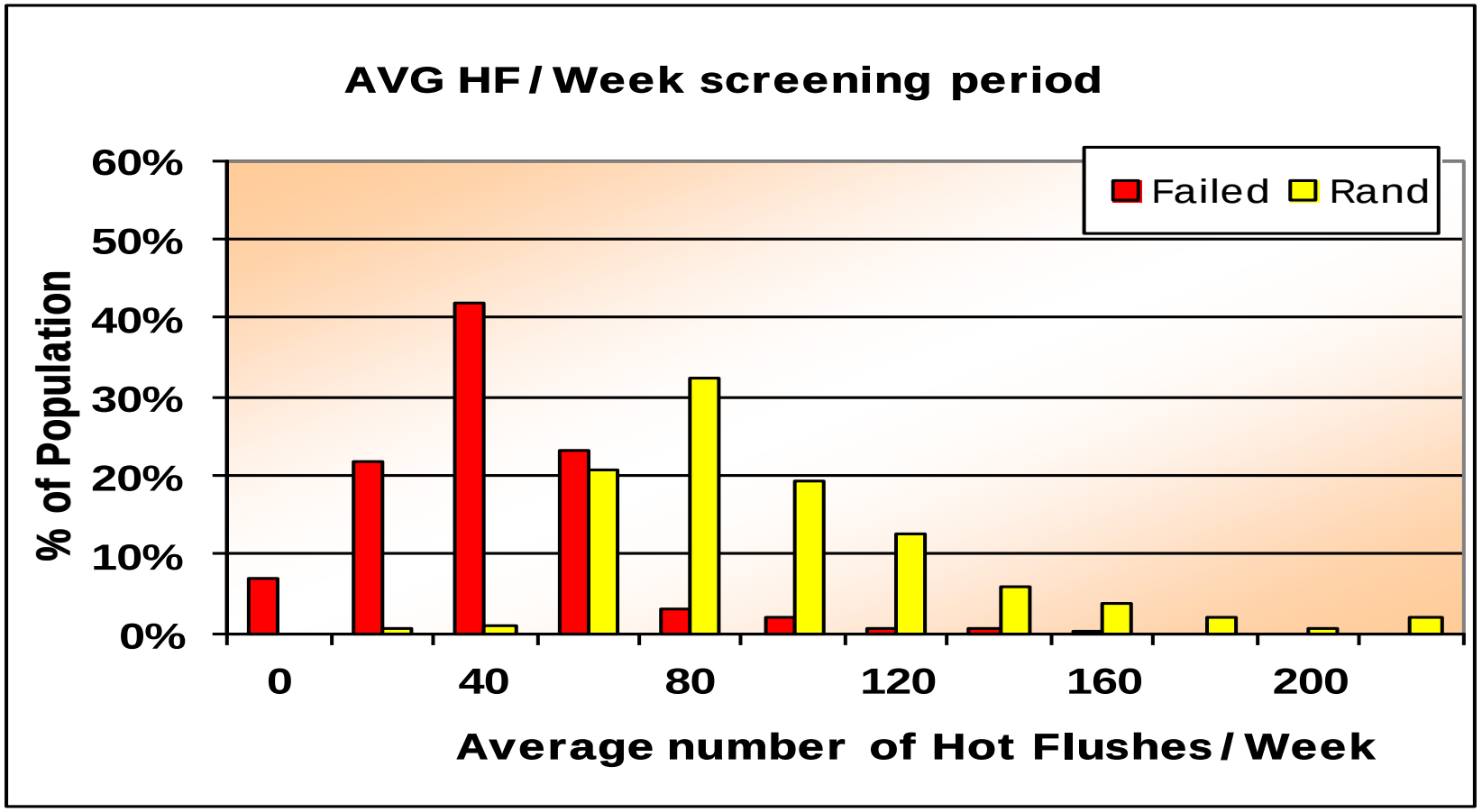
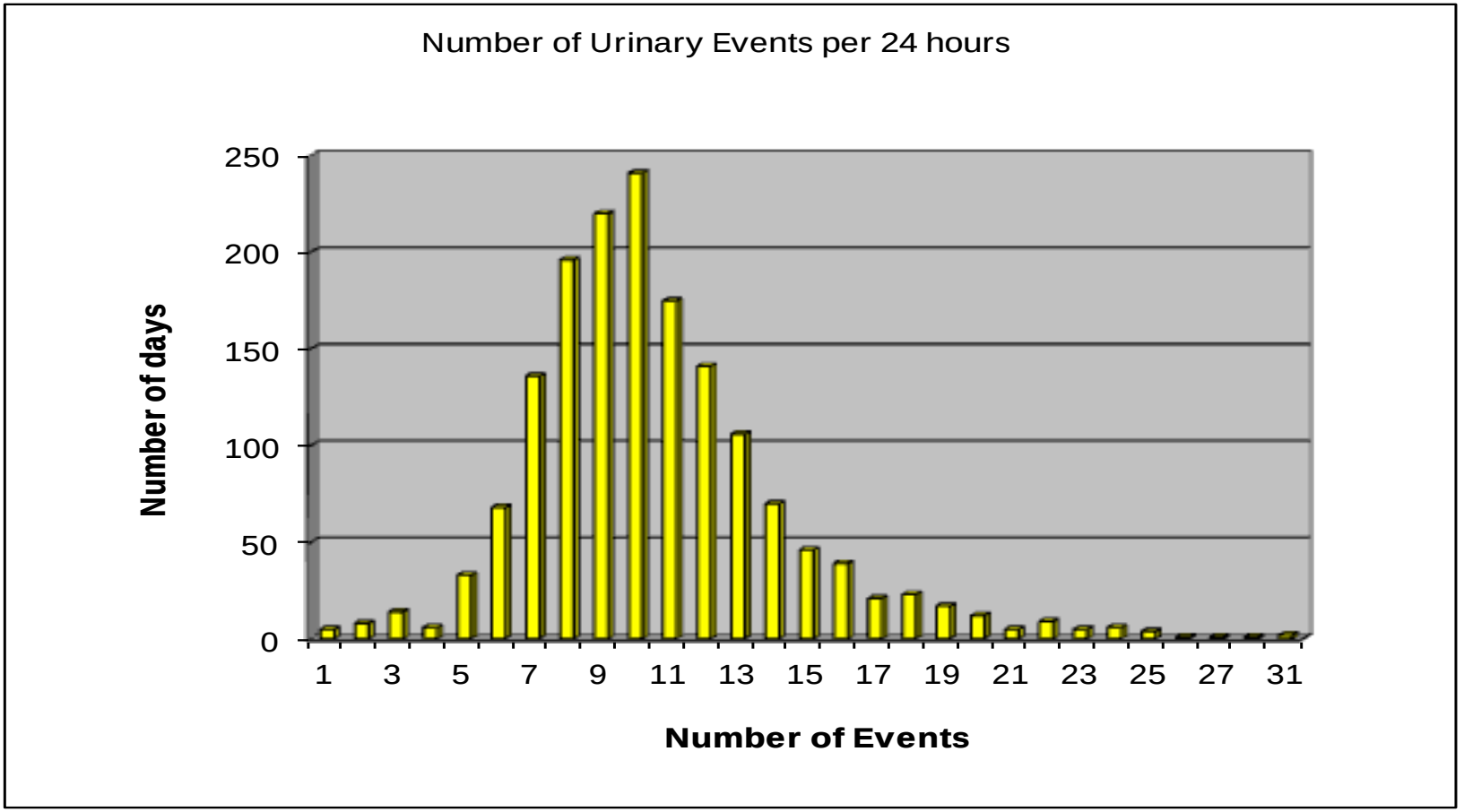
Combines objective and subjective data enriches voice of patient

Increased Quality / Ease of Collection



Flushes at the menopause

Increased Quality / Ease of Collection



Urinary Incontinence

Increased Quality / Ease of Collection

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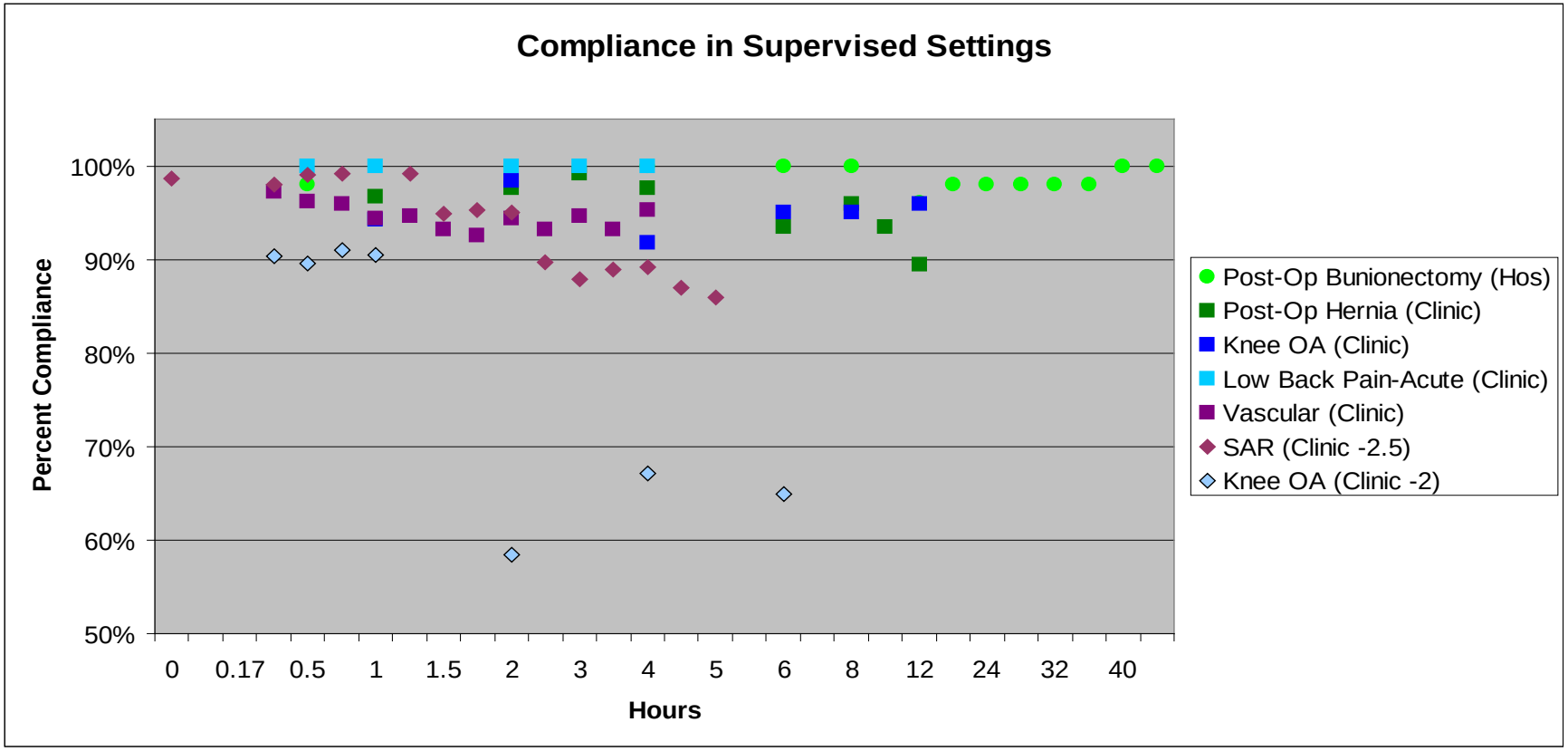
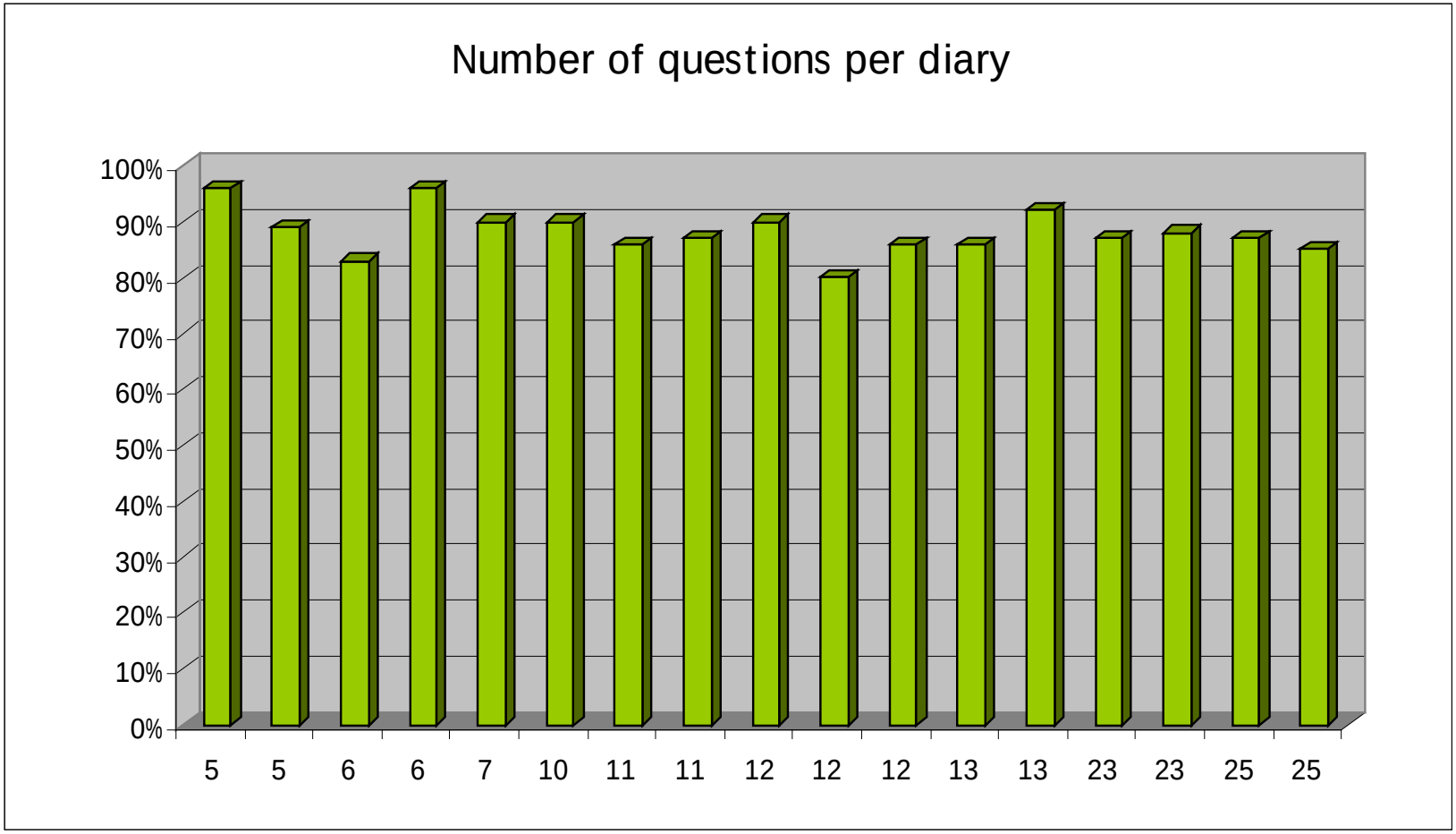
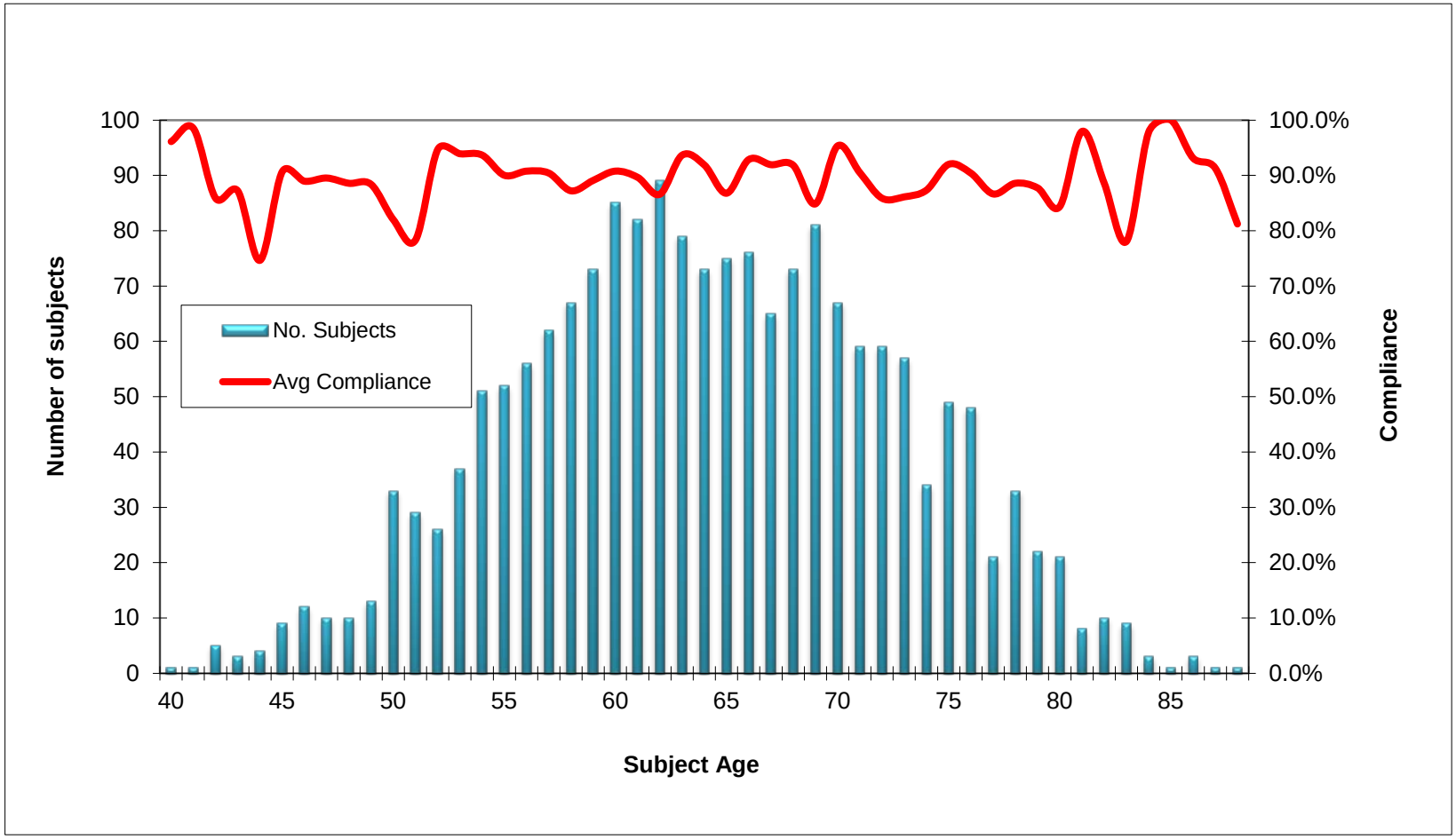
Timed assessments in various pain models



Increased Quality / Ease of Collection



Ease of collection has no age



Age has little / no affect on average compliance of diary completions

Ease of collection has no borders

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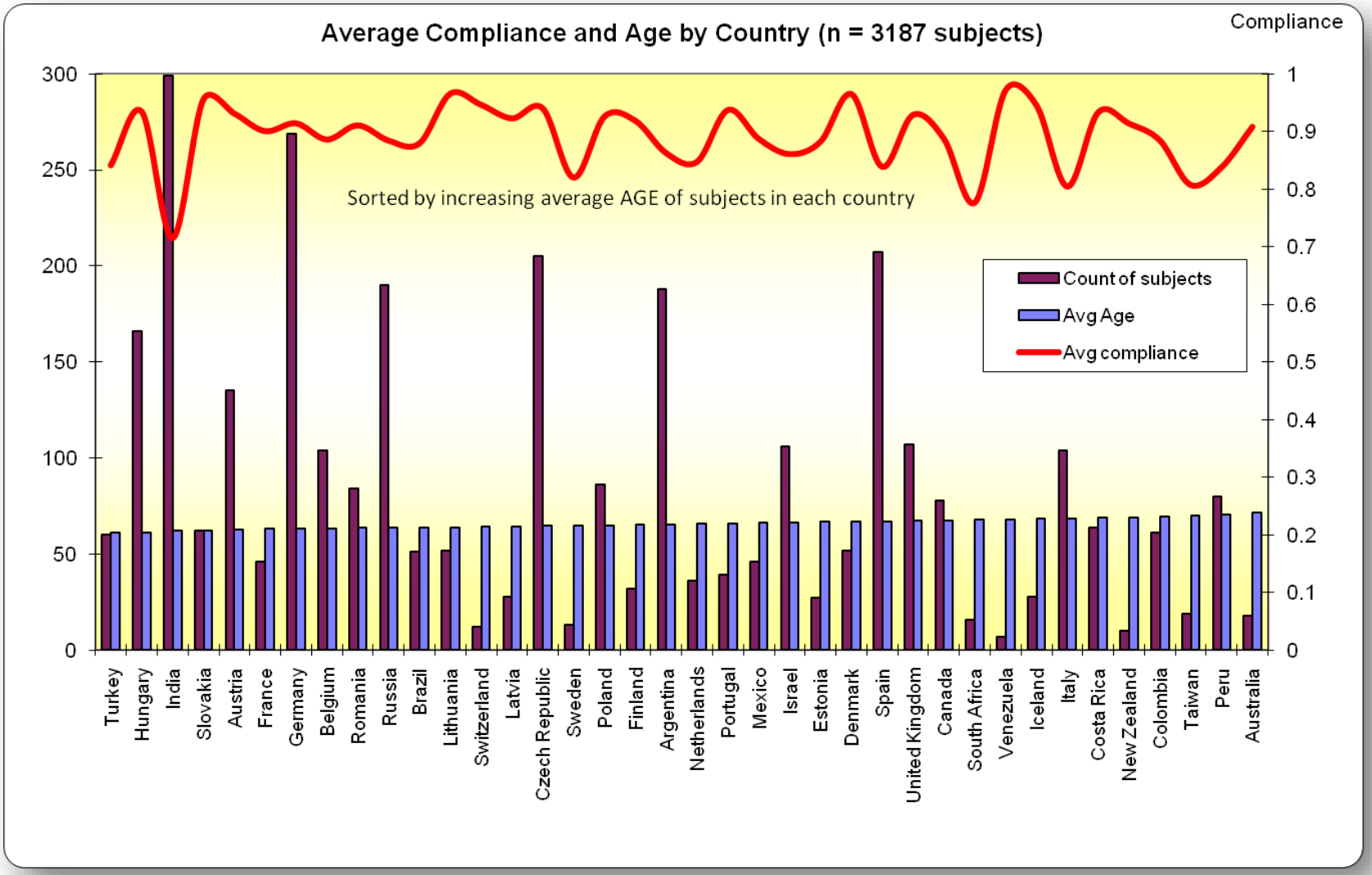
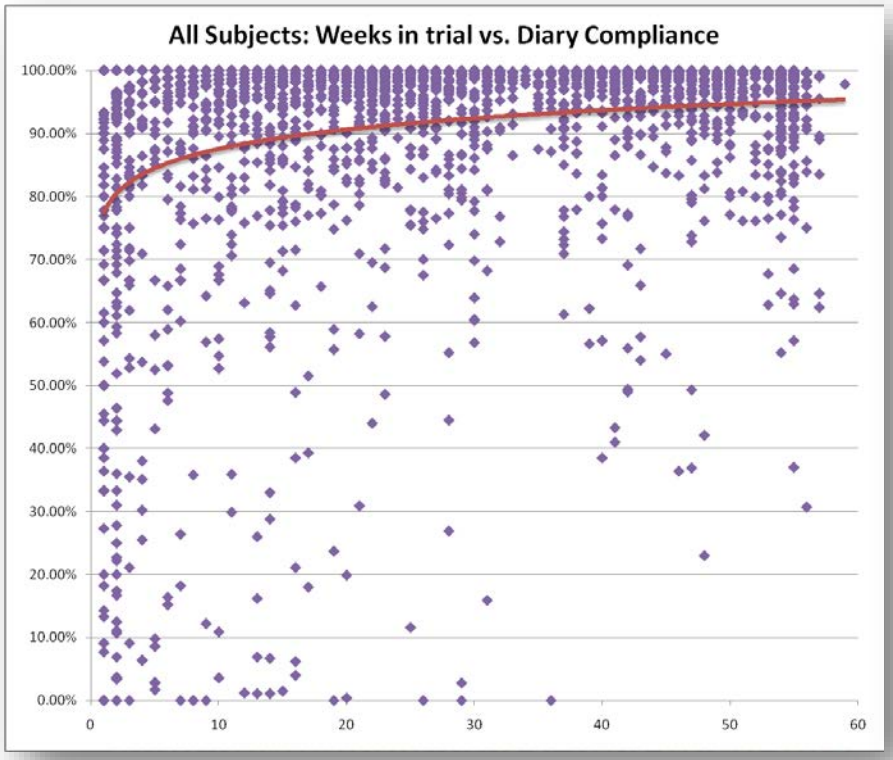
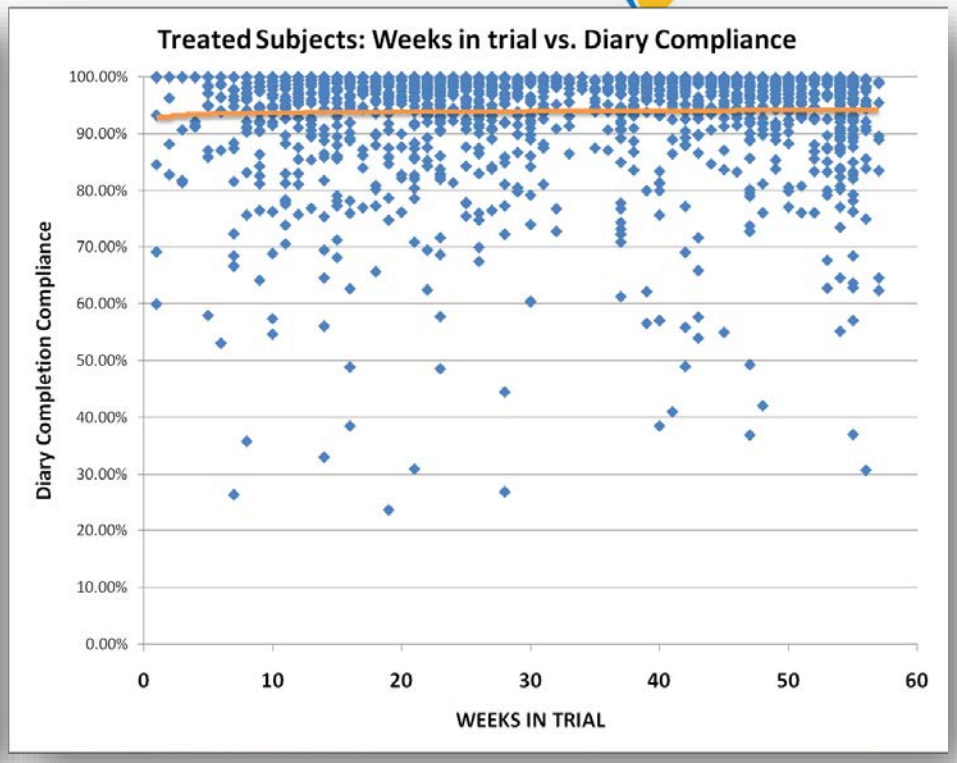


Ease of collection does not seem to stop





CONCLUSIONS: This analysis of the study meta-data is further proof that subjects can, and are willing, to complete daily diaries electronically. This is regardless of their age or country of origin. Additionally, the duration of participation in the trial is not a burden that has significantly impacted their ability to complete their diaries.

Shortened Recruitment / Decreased Drop-out

Study based on events rather than patients (COPD exacerbations, Migraine attacks, Bleedings in Hemophilia, Restless Legs Syndrome,…)

- need for 500 events
- based on events' occurrence in previous studies (paper diaries)
- planned recruitment of 14 months

Study Results

- 2 to 3 times more events than expected
- only 1 withdrawal of consent when much more was anticipated
- study ended 8 months earlier (recruitment of 6 months instead of 14)

Patients were asked why: The answer was that they behaved differently because of ease of use

New FDA Draft Guidance (1)

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Guidance for Industry

Irritable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2012
Clinical/Medical

New FDA Draft Guidance (2)

4. *Efficacy Measures*

Sponsors should choose a format for daily sign or symptom assessment (e.g., interactive voice response or personal digital assistant) so that patients can evaluate their IBS signs or symptoms on a daily basis throughout the trial. When assessing responses, sponsors should consider two distinct approaches: (1) examining the difference in average score (or average change from baseline score) between the treated and untreated groups; or (2) examining the difference in response rate in the treated and untreated groups, where the response is prospectively defined and represents an effect considered clinically meaningful. In many instances, an effective drug will have an effect on both measures.

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Q&A