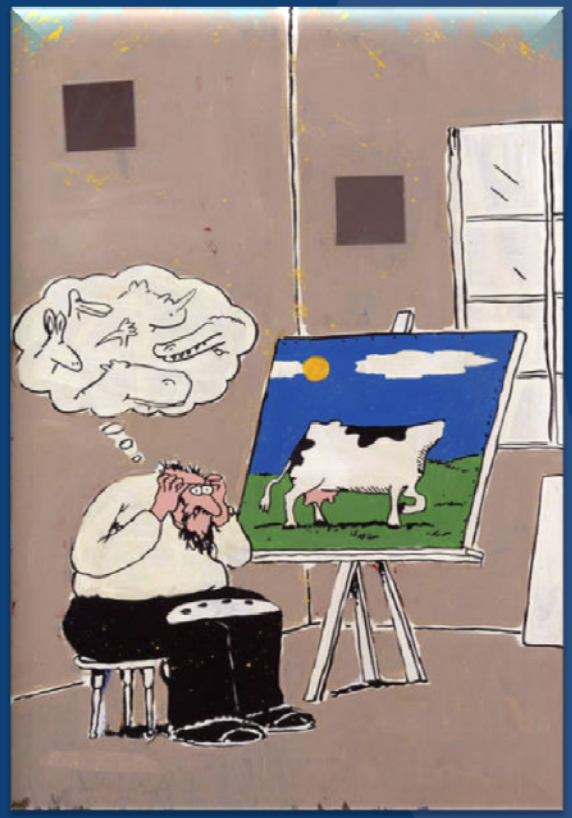


Patienten versus gesunde Probanden in frühen Studiendesigns – ein Überblick

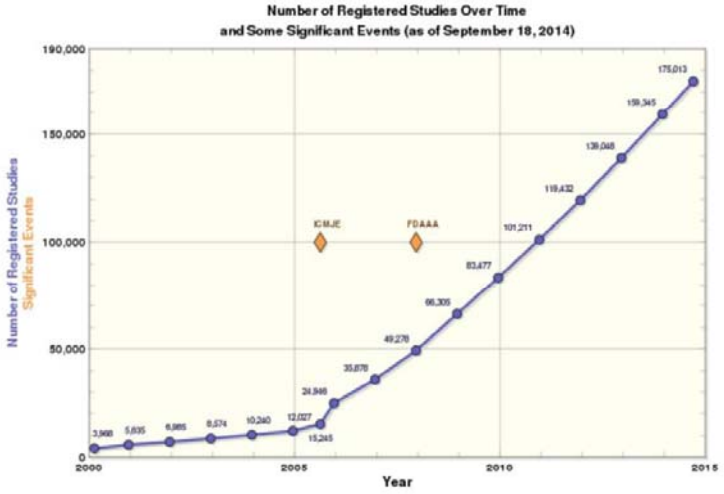
AGAH Workshop
Köln, 26. September 2014

cr.appliance

Dr.med. Robert Hermann, FCP
Clinical Research Appliance
Gelnhausen, Germany

Some Clinical Development Facts

- Over the last decade the number of compounds in development has increased by 62% and total R&D expenditures have doubled
- In 2012, 39 novel drugs classified as new molecular entities (NMEs) and biologic license applications (BLAs) were approved by the FDA
- Nearly 1000 projects in the industry's pipeline alone in oncology (ASCO 2012)



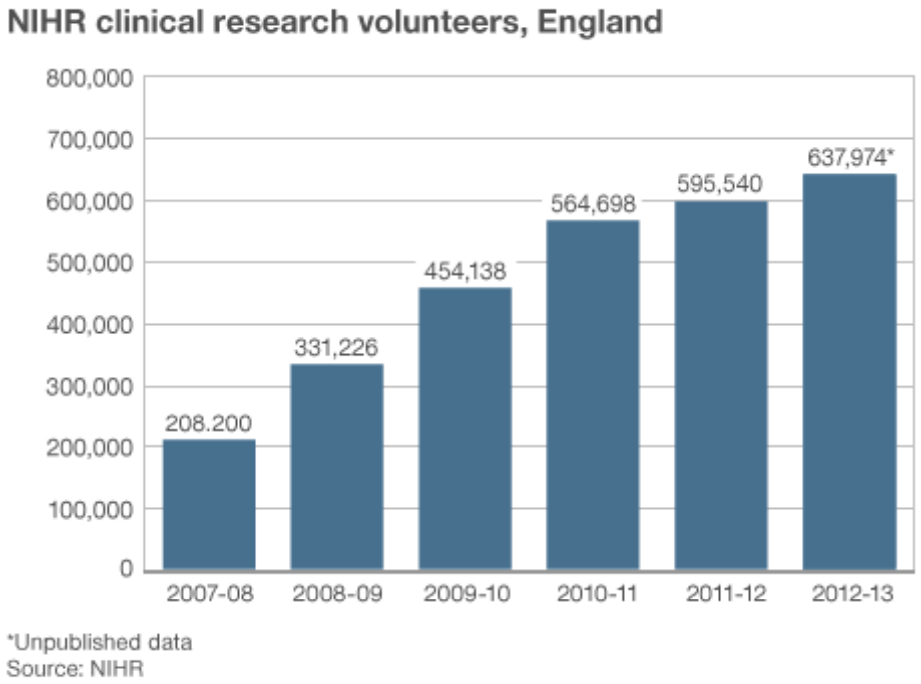
Source: http://ClinicalTrials.gov

- The number of trials run by CROs is increasing year on year and the value of the CRO market reached $13.6 billion in 2012
- Enrolling a patient can cost tens of thousands of dollars and it is currently estimated that 52% of patients drop out
- Increasing number of competing projects rapidly deplete volunteer patient pool

cr.appliance

Hay M et al. Clinical development success rates for investigational drugs. Nat Biotech 2014; 32: 40-51

National Institute for Health Research (NIHR) Data on Research Subjects

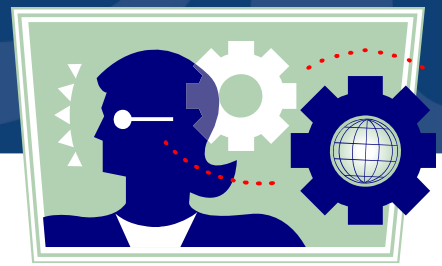


- The number of patients taking part in clinical trials in England has trebled in five years
- Figures from the National Institute of Health Research (NIHR) show almost 638.000 patients volunteered last year
- There are no exact figures for the number of healthy volunteers but the MHRA estimates about 8.000-9.000 take part in trials each year

Notable Industry move towards early patient studies with the aim of early „proof of principle“ (PoP) or „proof of concept“ (PoC) studies

cr.appliance

Current Clinical Development Mindset

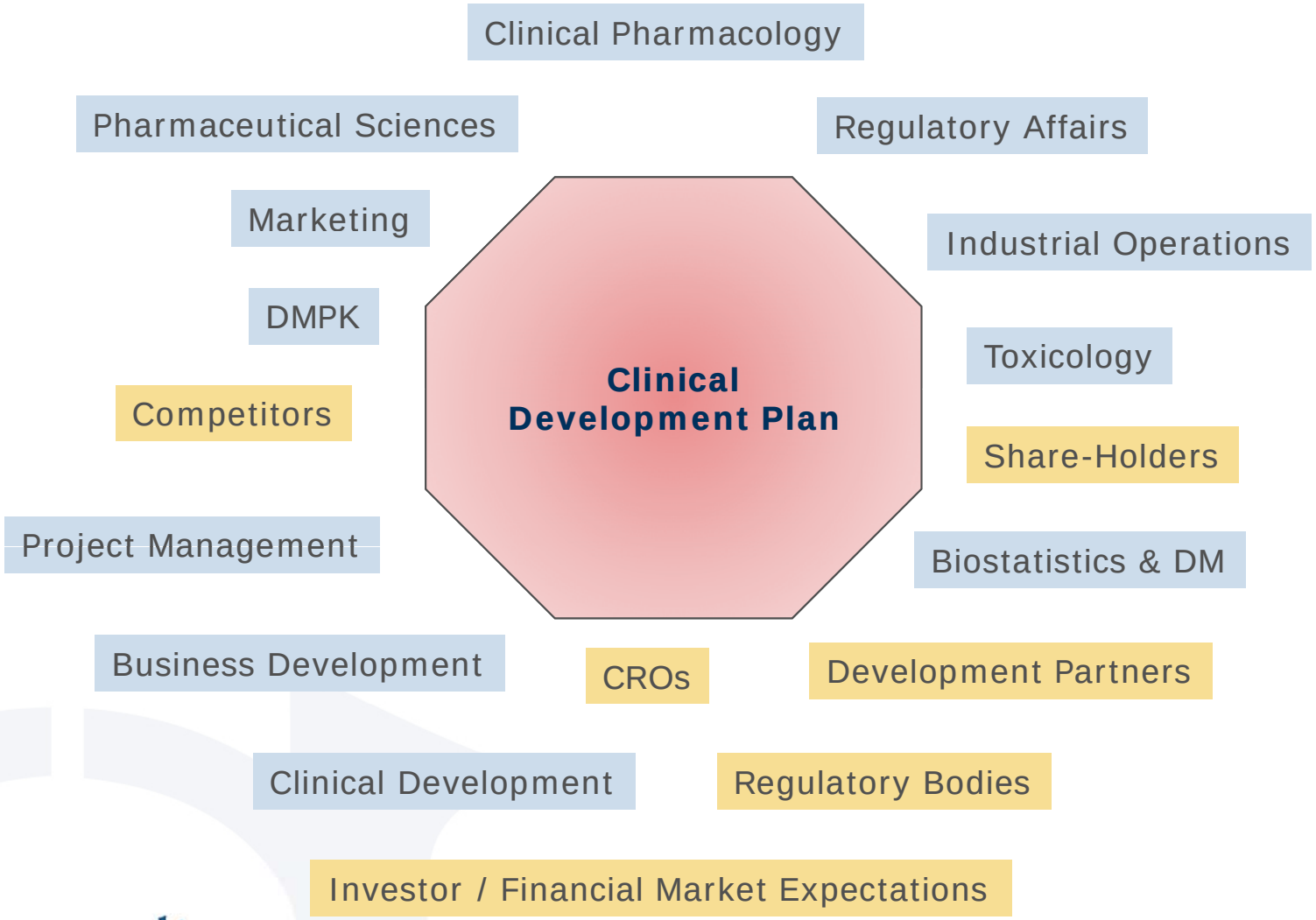


- The term mindset, refers to a set of established assumptions, methods or notations held by one or more people or groups of people;
- A “mindset” creates a **powerful incentive within these groups to continue to adopt or accept prior concepts, philosophies, behaviors, choices, or tools**;
- This phenomenon of **cognitive bias** is also sometimes described as **”groupthink”**, or a **“paradigm”**;
- It is often **difficult to counteract the effects of a “mindset”** upon analysis and decision making processes.

Clinical drug development is under the influence of the mindset of many stakeholders with conflicting targets!

cr.appliance

Many Internal & External Stakeholders – Clinical Drug Development is Not Pure Science



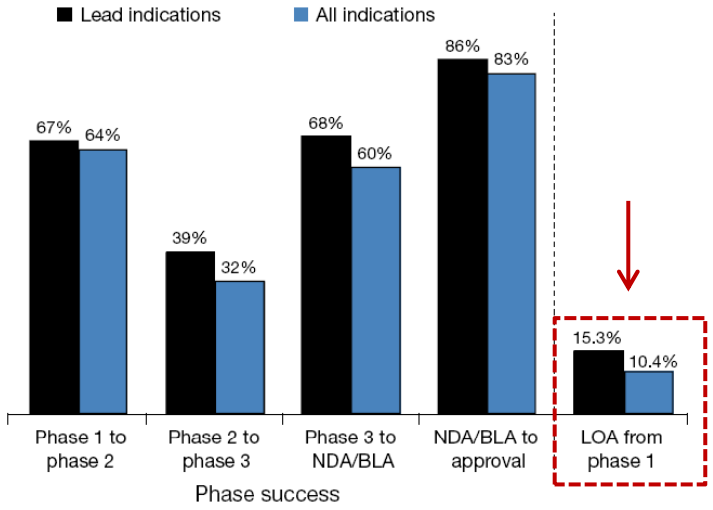
cr.appliance

Poor Efficiency in Drug Development Still Exists

The 90 % Rule….

- 90 % of targets fail in discovery
- 85% – 90 % of candidates fail in development
- Candidates fail in development mainly because of lack of efficacy or safety issues
- Only 1/7 to 1/3 of launched products recoup their R&D costs
- About 70 % of launched products could have been terminated in R&D with a NET benefit to the company

Phase Success and LOA Rates

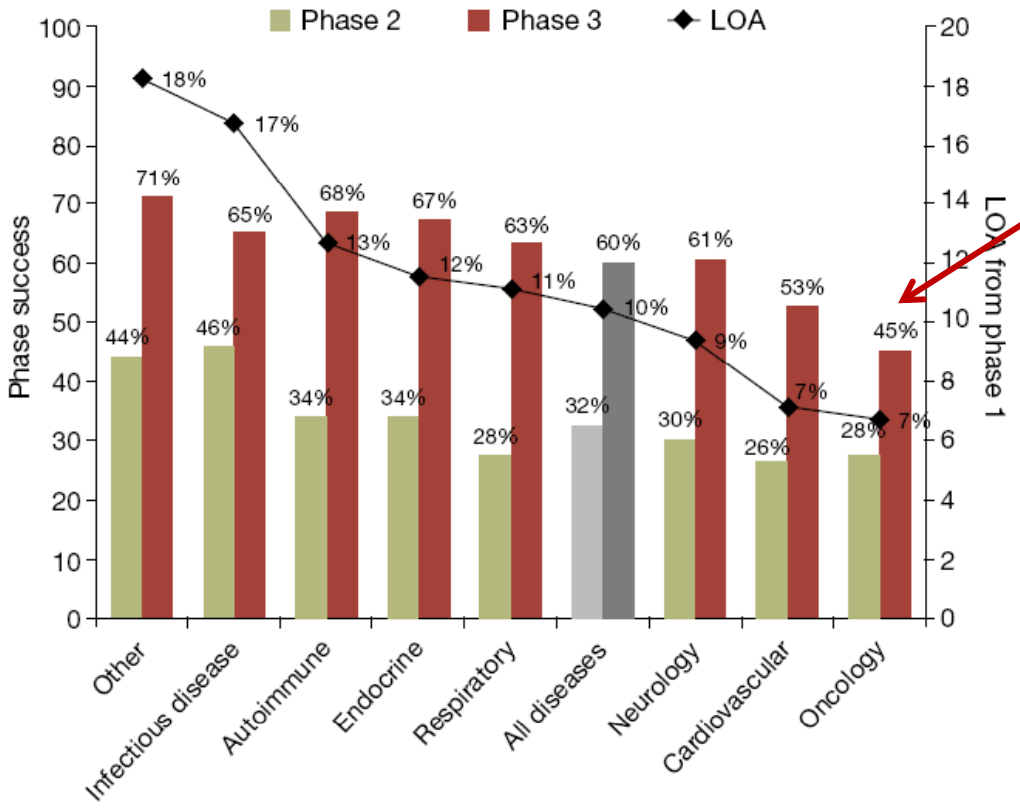


LOA = Likelihood of approval

Hay M et al. Clinical development success rates for investigational drugs. Nat Biotech 2014; 32: 40-51

cr.appliance

Clinical development success rates for investigational drugs



LOA = Likelihood of approval

The likelihood of approval of a Phase 3 Oncology product is less than flipping a coin!

This is a prototypical indication embarking early into patient studies!

What does this tells us about our drug development and decision making quality – and advantages of early patient studies?

cr.appliance

Hay M et al. Clinical development success rates for investigational drugs. Nat Biotech 2014; 32: 40-51

Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

- Amgen researchers tried to confirm published findings of preclinical oncology work ('Reproducibility of research findings')
- Fifty-three papers were deemed 'landmark' studies
- Nevertheless, scientific findings were confirmed in only 6 (11%) cases
- Similarly, team at Bayer HealthCare* reported that only about 25% of published preclinical studies could be validated to the point at which projects could continue
- More troubling, some of the research has triggered a series of clinical studies — suggesting that many patients were subjected to a trial of a regimen or agent that probably wouldn't work
- ➔ emerging IRB requirements of futility analyses in early cancer studies

cr.appliance

Begley CG et al. Nature 2012; 483: 531-33

*Prinz F et al. Nature Rev Drug Discov 2011; 10: 712

Pharmaceutical Companies Don't Place Enough Emphasis on Early 'Learning Trials' for Their Developmental Products

Exploratory Trials

Confirmatory Trials

CLINICAL PHARMACOLOGY & THERAPEUTICS

VOLUME 61 NUMBER 3 MARCH 1997

COMMENTARY

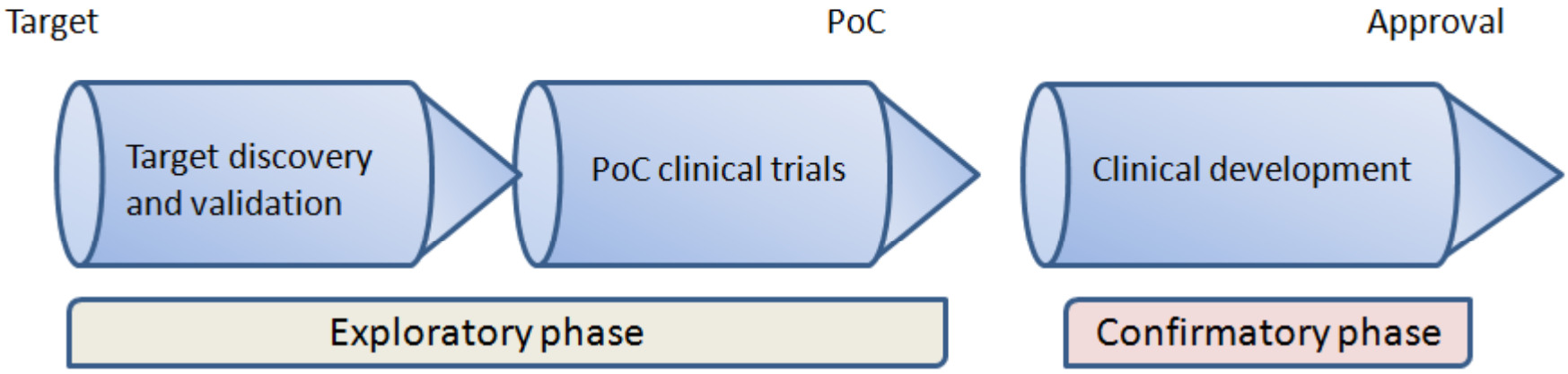
Learning versus confirming in clinical drug development

Lewis B. Sheiner, MD *San Francisco, Calif.*

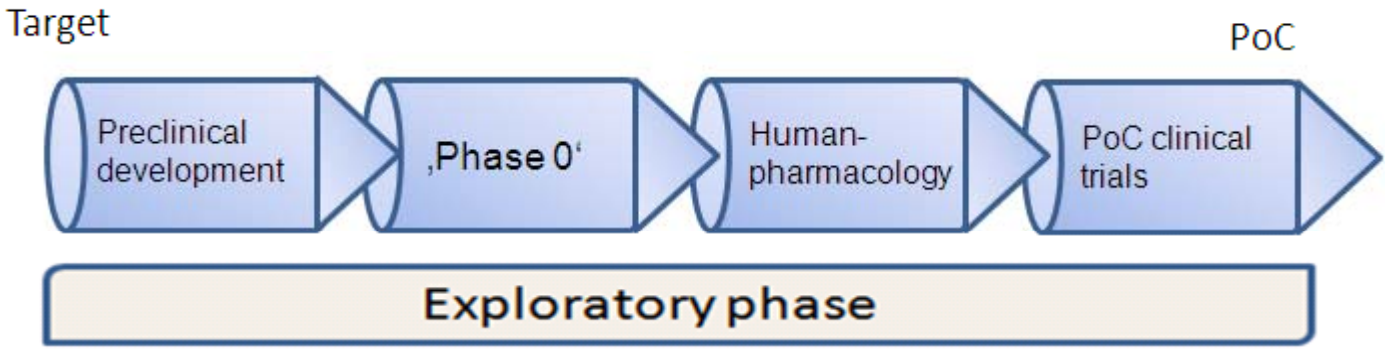
- Exploratory CD consists of early studies in humans to address key issues identified as critical to the development of a successful drug (i.e. "risk-management exercise")
- Full development with all its inherent costs and commitments proceeds only after targeted and careful evaluation of apparent development risks, with significant limitation of remaining risks

cr.appliance

Be Watchful With Published “Innovatory DD-Concepts”: May Not be Validated and Just Reflect Partial Interests of Certain Disciplines.



Concept proposed by Orloff J, et al.: Nature Reviews Drug Discovery | AOP, published online 9 October 2009



Still applicable early drug-development paradigm after “reality check”

cr.appliance

Early Patient Studies Implying Early Phase Transition to Phase II

Premature Phase Transition (e.g. Phase I ➔ II) creates a false notion of project progress

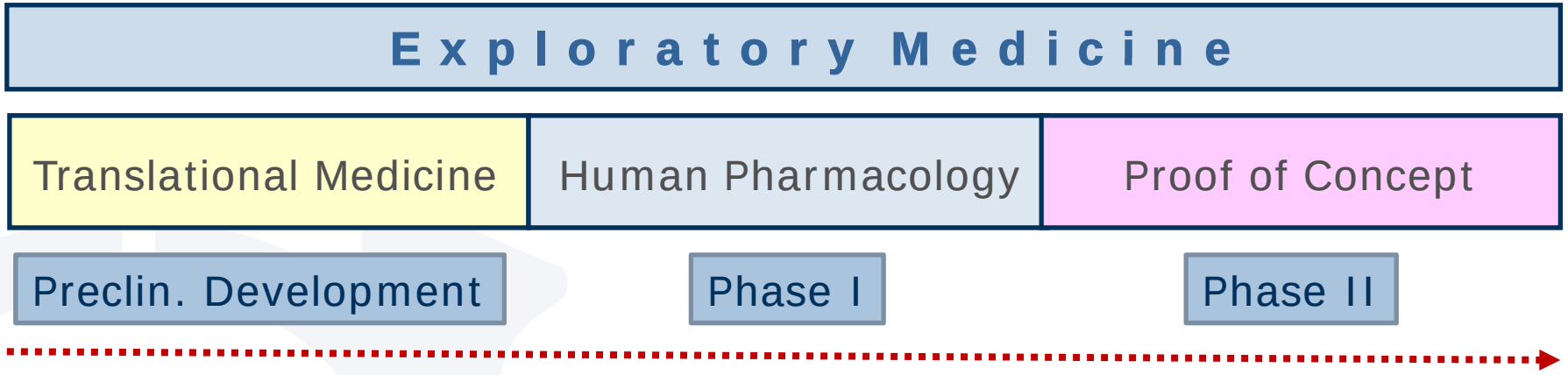
Taking a train that starts earlier must not necessarily mean that one arrives the targeted destination faster

- Speediness in setting up a CDP or study is frequently confounded with faster approval
- Earlier submission of NDA to regulatory bodies is often confounded with faster "time to market"

cr.appliance

From the Pre-Clinical/Clinical Interface to Phase IIa: From “Phase 0” to “Proof of Concept” (PoC)

- Translational Medicine („from bench to bedside“)
- Exploratory IND Trials / „Phase 0“ / Single Microdose Studies
- **Human Pharmacology** / Clinical Pharmacology
- Exploratory Medicine
- Experimental Medicine
- Proof of Mechanism (PoM), Principle (PoP), Concept (PoC),



cr.appliance

Studies in Healthy Adult Subjects are still the Backbone and at the Heart of Early Clinical Drug Development

- Basis for go/no go decision or safety provisions before the start of Phase II in patients:
  - safety/tolerability
    (safe dose range, AE profile of common AEs)
  - PK including critical drug interactions & food-drug interactions
  - Identification of human metabolic routes & transporter-based disposition
  - PD effect and critical drug interactions

- Support selection of
  - dose, formulation, dose regimen, route
  - …informing posology in target patient population
- Impact on positioning / provide USP (marketing support)

Nota bene: more than 50 % of SmPC provided by phase I

cr.appliance

Clinical Study Classification According to Objective

Phase I	Phase II	Phase III	Phase IV
Human Pharmacology	**Therapeutic Exploratory**	**Therapeutic Confirmatory**	**Therapeutic Use**
• Assess tolerance • Define/describe PK and PD • Explore drug metabolism and drug interactions • Estimate activity	• Explore use for the targeted indication • Estimate dosage for subsequent studies • Provide basis for confirmatory study design, endpoints, methodologies	• Demonstrate /confirm efficacy • Establish safety profile • Provide an adequate basis for assessing the benefit/risk relationship to support licensing • Establish dose-response relationship	• Refine understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendation

*Typically done in healthy subject studies ➔ less constraints, easier, cheaper and faster

cr.appliance

Federal Register / Vol. 62, No. 242 / Wednesday, December 17, 1997

CODE OF PRACTICE

The widely adopted rationale for the use of healthy volunteers in Phase I trials is explained in the Association of the British Pharmaceutical Industry (ABPI) guidelines for Phase I Clinical Trials, which delineate them as easier to find than patients with specific conditions,

- free of other medicines,
- more likely to respond uniformly,
- and better at completing long and complex trials.

The ABPI guidelines go on to suggest that some trials should involve only patients with the target disease due to safety and ethical reasons.

cr.appliance

Studies in Healthy Adult Subjects are still the Backbone and at the Heart of Early Clinical Drug Development

Issue: Investigation of Drug-Drug Interaction Potential

- EMA:" Knowledge about the interaction potential should be gained as early as practically possible to assure safety during clinical **phase II** and III studies, as well as during clinical use after approval."
- This implies that Sponsors need to do either their DDI "homework" prior to embarking in early patient trials or need to generate long lists of disallowed concomitant medications in the study protocol (which hinders and complicates patient recruitment)
- Mechanistic DDI studies allowing extrapolations to other drugs are typically done in healthy subjects

Only when the required knowledge base for patient studies is properly established, smooth & unhindered patient recruitment can be expected!

cr.appliance

EMA DDI GL on the Need of Food Effect Studies

Effects on the new IMP

Recommendations on timing of food interaction studies

- Too many phase III trials take place before food interaction knowledge is available
- If the drug has been administered without concomitant food recommendations and there is a large food effect, the overall outcomes are unreliable and unsatisfactory

→ Food recommendations needed!

cr.appliance

Points to Consider in Early Patient Studies – Are Food Effects Properly Examined at this Point in Time?

Patients can hardly be subjected to similar rigorous food restrictions as compared to healthy volunteers!

- Abiraterone (Zytiga): AUC↗ 1000%
- Bosutinib (Bosulif): AUC↗ 130%
- Erlotinib (Tarceva): AUC↗ 100%
- Lapatinib (Tyverb): AUC↗ 325%
- Nilotinib (Tasigna): AUC↗ 80%
- Pazopanib (Votrient): AUC↗ 100%
- Regorafenib (Stivarga): AUC↗ 48%
- Vemurafenib (Zelboraf): AUC↗ 370%

Exposure increases in fed state

Label:
- fasting (= at least 1 h before / 1-2 h after meal)
- with/after meal
- without regards to meal

cr.appliance

Possible Cascade of Food-Effect Studies According to EMA GL

Food study with high calorie / high fat meal

No sign. food effect: Phase II/III without food restrictions

Sign. food effect

Food study with lighter meals

Food study at different times before / after meal

Food recommendations for Phase II/III studies

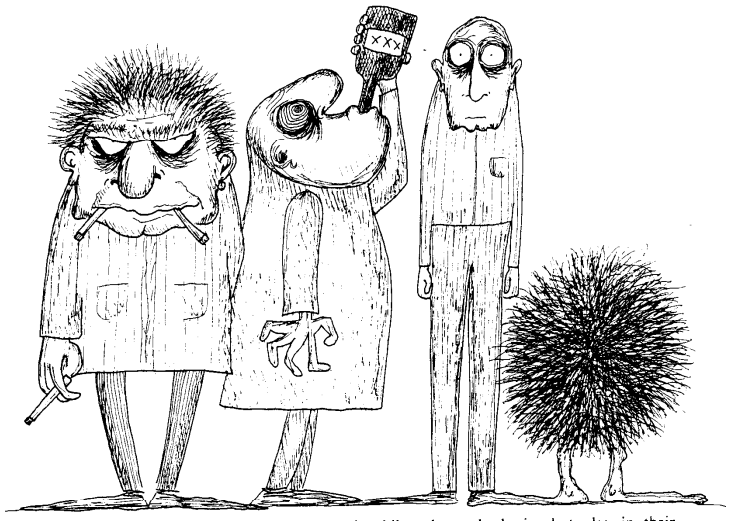
Note: In case of formulation switch an additional food effect study needs to be conducted with the final formulation

cr.appliance

Early Patient Studies often not Sufficiently Powered for Existing Patient Diversity / Heterogeneity

Patient Population(s)

- Responders oder non-responders known /identifiable?
- Outliers / heterogeneity in PK and/or PD due to intrinisc factors known? (gender, ethnicity etc.)
- Information about other, e.g. disease phenotypes known?
- Genetic polymorphisms known?
  - PK-based (enzymes, transporters)?
  - PD-based (Efficacy or Safety?)



cr.appliance

Intersubject Variability in Drug Response to be Considered

- It is unusual for a drug to work optimally in each and every individual;
- 20% to 75% of subjects in 14 major clinical trials appeared to derive no clinical benefit from treatment

Creates uncertainty in decision making based on small scale early patient trials

"They say we're not placing enough emphasis on diversity."

Source: Kenneth Thummel
Washington State Board of Health
Genetics Task Force Meeting, 2002-04-12
http://www.doh.wa.gov./sboh/Priorities/Genetics/GTF2002_04_12/Tab03_KT-pptslides.pdf

cr.appliance

Protocol Feasibility and Site Selection – What are the Issues?

Most patient studies do not complete on schedule, causing

- direct increased costs for additional sites, project management, etc.
- delayed development programme / partnering / exit
- impact on the product's NPV

How big is the problem?

- 60% of protocols need amendments and on average there are 2.3 amendments per protocol[1]
- 93% (USA) to 82% (Europe) of studies completed late in 2007[2]
- Average delay was 4.6 months[1]
- Delays cost - $35K per day per trial[3]

1 CISCRP 2006
2 CenterWatch 2007
3 Promodel white paper: simulation solutions for clinical trials; McKinsey and IBM 2002

cr.appliance

Clinical Operations' 'Big Five'

Too much haste, not enough speed

- Leaving corrective action too late when blown off track
- Choosing the wrong service providers
- A protocol that is scientifically sound but not feasible and requires amendments
- Selecting the wrong investigator sites and needing to add more to compensate

cr.appliance

Lasagna's "Law"

The number of patients predicted by investigators typically falls by up to 90% at the start of a study"

"Only to re-appear as soon as the study is over"

Dr Louis Lasagna (1923-2003)
Physician and Clinical Pharmacologist

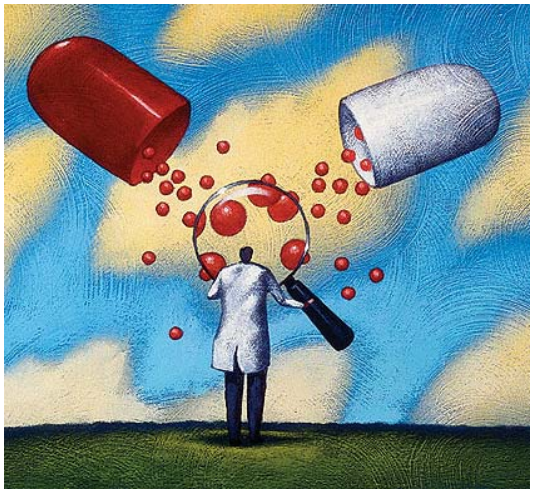
In 1964, he wrote a modernized version of the Hippocratic Oath which emphasized a holistic and compassionate approach to medicine

He played an important role in reshaping the pharmaceutical industry, being the first to demonstrate the necessity of placebo-controlled clinical trials

He was a constant scrutiniser of the high cost of drug development

cr.appliance

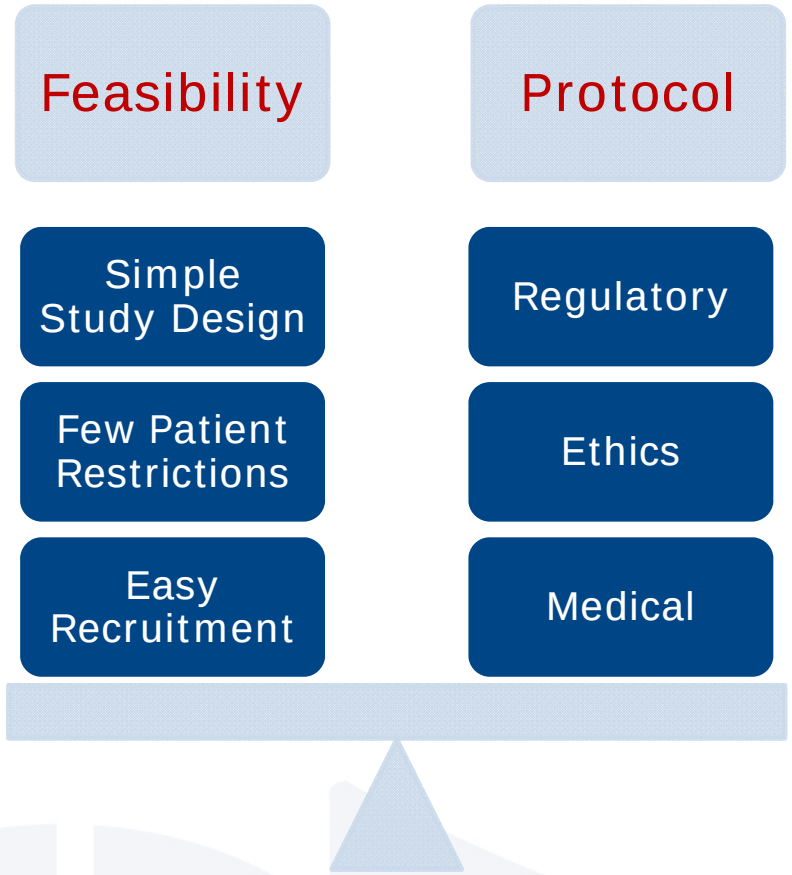
Common Problems with Protocols of Early Patient Studies



- Protocol not well aligned with clinical practice
- Acceptability of Placebo-control in target patient population & indication
- Acceptability of withdrawal of established treatments
- Compliance with standard of care while the study is running
- Other protocols compete for same patient population
- Inclusion / exclusion criteria are usually strict in early clinical trials
  ➔ only a small fraction of the target population eligible
- Allowed and disallowed concomitant medications & food restrictions
  ➔ prior DDI and food-drug interaction studies required
- Procedures are too onerous for the site
- Patients reluctant to consent to too complex protocols with too many restrictions

cr.appliance

Conflicting Demands & Requirements in Early Patient Trials



- Regulatory, ethical and medical hurdles are generally higher for P studies as compared to HS studies
- Lead times are longer
- Knowledge of critical product characteristics is limited in early clinical trials, thereby hampering "relaxation" of inclusion/exclusion criteria (e.g. drug-drug and food-drug interaction knowledge)
- Restrictions (concomitant drugs, diet, lifestyle) cannot be applied with the same rigour to P as it is possible in HS

Sponsors need to understand and accept the broader knowledge base that is required for early P trials, to allow for an unhindered and safe recruitment of an unbiased target patient population

cr.appliance

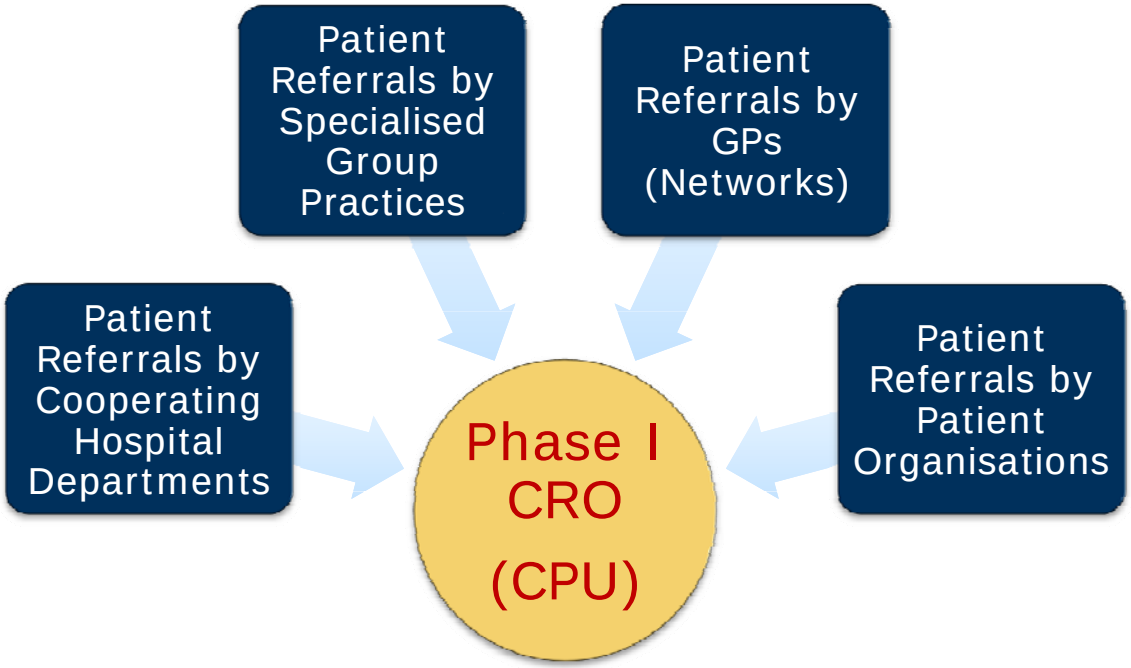
Common Problems with Site Selection & Patient Recruitment in Multi-Center Clinical Trials

- KOLs often do not have enough patients
- … and usually have competing protocols
- Clinical sites over-promise
- Numbers of patients meeting protocol criteria not checked
- Monitors focus on GCP and documents, not patient recruitment
- Insufficient focus on / reward for the people that will do the work
- Site has no active recruitment plan, waits for patients to show up at the clinic

Patient enrolment, retention, and compliance are among the biggest challenges in carrying out clinical trials swiftly and within budgets.
Patient centric approaches needed!

cr.appliance

Model of a Patient Centered Phase I Like, Mono-Centric, Study Concept for Early Clinical Trials in Patients



- Clinical centres are unburdened from administrative tasks and can focus on patient recruitment
- Phase I CRO assumes role of CPU and SMO for recruiting centres at the same time
- Phase I CRO must adopt processes and environment to patient needs, i.e. is responsible for patient well being and retention

- Access to patients via therapeutic area experts/patient's treating physicians
- Study-specific information material by CRO
- All administrative burden and GCP-compliance aspects assumed by CRO
- Sponsor contact and contractual issues managed by CRO
- In-house periods managed by CRO
- Ambulatory visits either by CRO or referring medical expert / clinical site

cr.appliance

Benefits of a Single Versus Multicenter Approach in Early-Phase Patient Studies

A Case Study of Multiple Sclerosis Patients

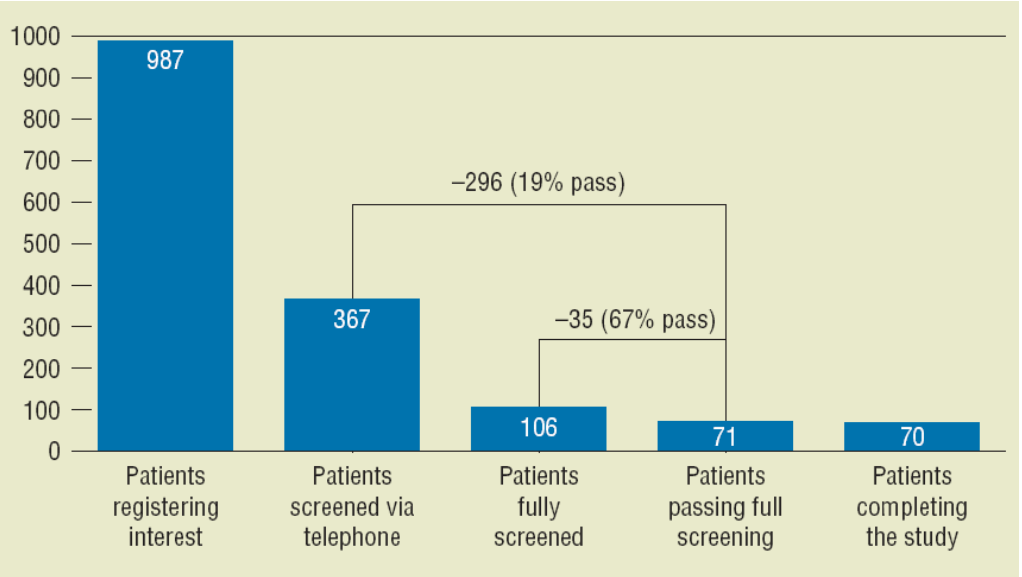
- Case example of a successfully conducted monocentric trial in N=71 recruited MS patients (RRMS)
- Study provided no therapeutic benefit to patients
- Recruitment rate of 11.8 patients/month
- Excellent patient retention (only 1 drop-out)
- Success factors highlighted:
  - Dedicated subject recruitment division
  - Efficient pre-screening of patient eligibility by telephone interviews
  - The provision of staff and tools with dedicated function

cr.appliance

Berelowitz KS, Wolf C, Täubel J.
Benefits of a Single Versus Multicenter Approach in Early-Phase Patient Studies. Monitor October 2011

Recruitment and Screening Selection Effort Involving Enrollment of 71 Subjects

- Sponsors remain cautious about running larger early-phase patient trials in a Phase I setting
- Predominantly due to apprehensions over the ability of single-center sites to recruit large patient panels
- Also doubts on the tolerance of the target patient populations for the typical environment and intensity found in Phase I studies and CPUs



- The case study shows that the use of a single-center, early-phase trial setting with patients is not only possible, but has benefits over the widely accepted multicenter approach taken by many sponsors in an attempt to mitigate the perceived risk associated with the conduct of a clinical trial at just one site

cr.appliance

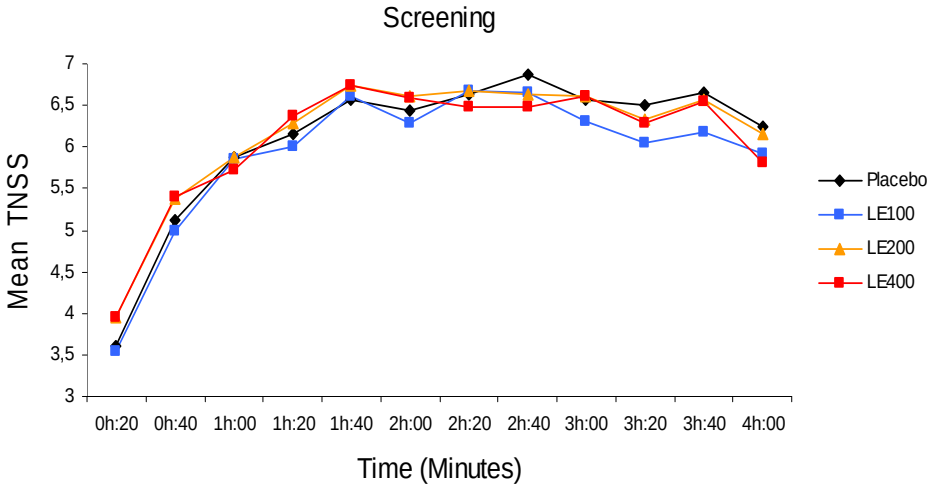
Berelowitz KS, Wolf C, Täubel J.
Benefits of a Single Versus Multicenter Approach in Early-Phase Patient Studies. Monitor October 2011

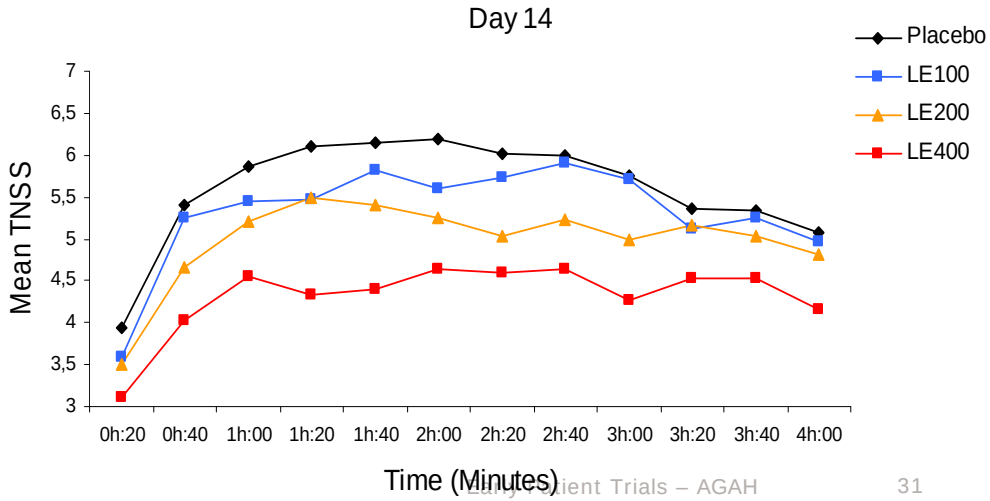
Allergic Rhinitis Allergen Challenge Phase-IIa Study in an Environmental Exposure Unit (Allergen Challenge Chamber)

Study Design Summary

- Mono-centre study:
  165 subjects with SAR
  (84 males, 81 females)
- Double-blind, placebo-controlled,
  parallel group design
- Treatment with single daily doses of
  100 µg, 200 µg, 400 µg Loteprednol
  nasal spray or placebo for 14 days
- Allergen challenge with 4000 pollen/m³
  for 4 hours on a screening day and
  on days 7 and 14
- TNSS, nasal flow, nasal secretion,
  lung function

Krug N, et al.: Allergy 2005; 60:354-59



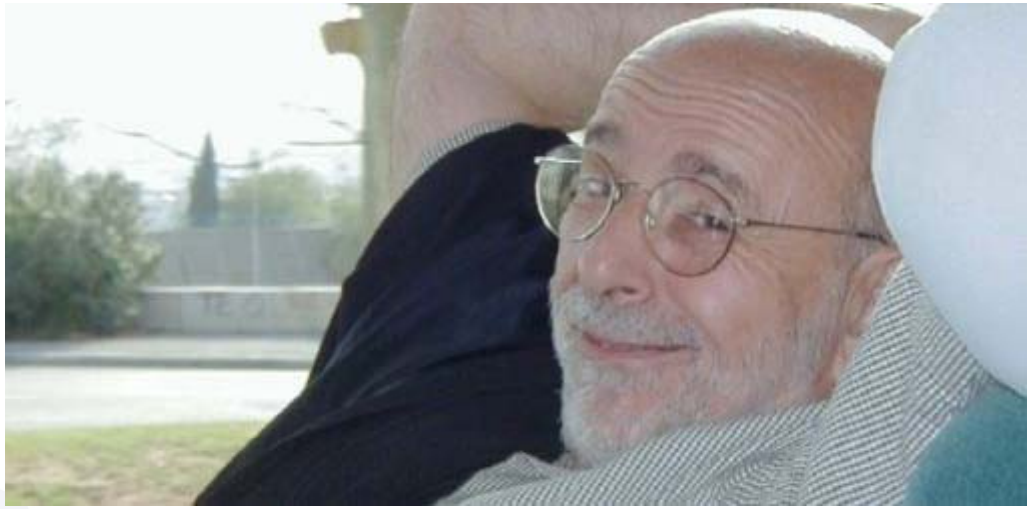


cr.appliance

Key Issues in Drug Development – The Questions We Ask !

„The intellectual illness of clinical drug evaluation that I have discussed here can be cured, and will be cured when we restore **intellectual primacy to the questions we ask**, **not the methods by which we answer them**.“

Lewies Sheiner



Sheiner, L.B. The intellectual health of clinical drug evaluation. *Clin. Pharmacol.Ther.* ***50, 4–9 (1991).***

cr.appliance