In-house non-therapeutic patient trials in a Phase-I Setting – Practical Requirements

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Phase II trials in a Phase I setting

Faster into patients - for a literally clinical early development

- Advantages:
  - High throughput of volunteers from a target population
  - Early clinical proof of concept
  - Fast Go-/No-Go-decisions including target PD information
  - Use of a highly standardized environment with close-to-zero data loss

- Disadvantages
  - Does it work at all?

Phase I and patient care: two worlds

Phase I:

- CRO- or Pharma-driven
- Industry-based standards
- Integrated quality management
- Focus on delivery of scientific results

Patient care:

- (university) hospitals or out-patient practices
- Clinical trials are secondary business
- Quality management for standard services
- Focus on curative needs

Best of both worlds needed to perform early patient trials

Two worlds: how can they connect?

- Establishing Phase-I facilities in university hospitals
  - Examples for Germany: Berlin, Bonn, Lübeck
  - Advantages: Proximity to medical specialists and patients with the clinic network
  - Problem: Little access to „bread-and-butter“ studies in the early IMP development phases (PK, bioequivalence, DDI, FDI) due to lack of extended healthy volunteer database

- „Joint ventures“ of practitioners and Phase-I-CROs
  - Examples for Germany: Cologne
  - Advantages: synergy of experiences, access to trial-naïve patients
  - Problem: Communication intensive construction, difficult division of responsibilities

The „joint venture“ concept

Practitioner with private practice and Phase-I CRO in close proximity

- Practitioner contributes with
  - **special medical expertise**
  - access to patients within the indication
  - ambulatory services, screening, follow-up examinations

- CRO contributes with
  - **GCP expertise**
  - site management for trial specific methods
  - raw data /CRF management
  - in-house services, additional staffing of the ambulatory practice

➢ **Two distinct facilities, one site**

Challenges of the joint venture concept

- Close communication between both partners is crucial
- Division of responsibilities
- Main objective of the study should lead to the decision for role of principal investigator
  - Indication-specific objective: medical specialist
  - Design/Drug-specific objective: clinical pharmacologist
- Conception of clinical trial site by common standard operating procedures
- Custom site description including both partners for ethical review of site feasibility

It‘s all about the patients

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How do clinical trial sites recruit?

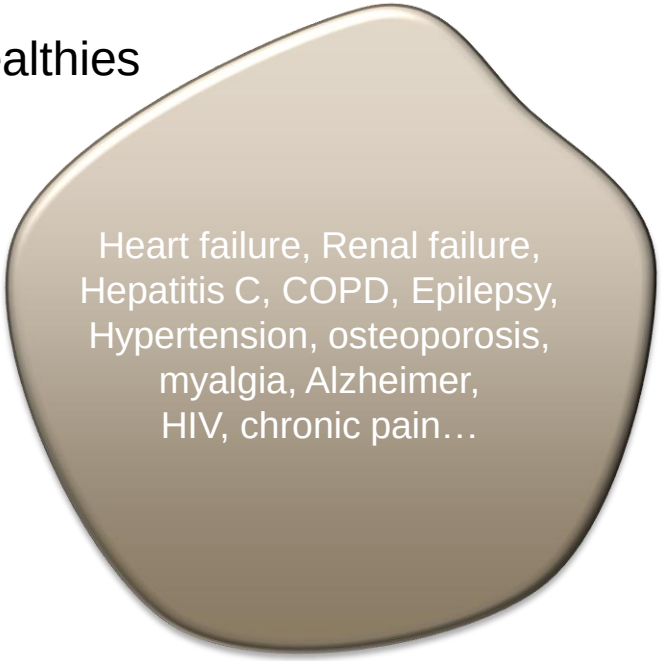
- Phase I CRO
  - „All at once“
  - Database supported /advertisements
  - Favourably preparation and appointment of subjects for group-wise information and treatment
  - ➢ Trial-centered approach
- Clinical site
  - „One at a time“
  - Based on treated population and spontaneous appearance of patients due to medical need
  - Start of treatment individually planned for each patient
  - ➢ Patient-centered approach

Population Structures

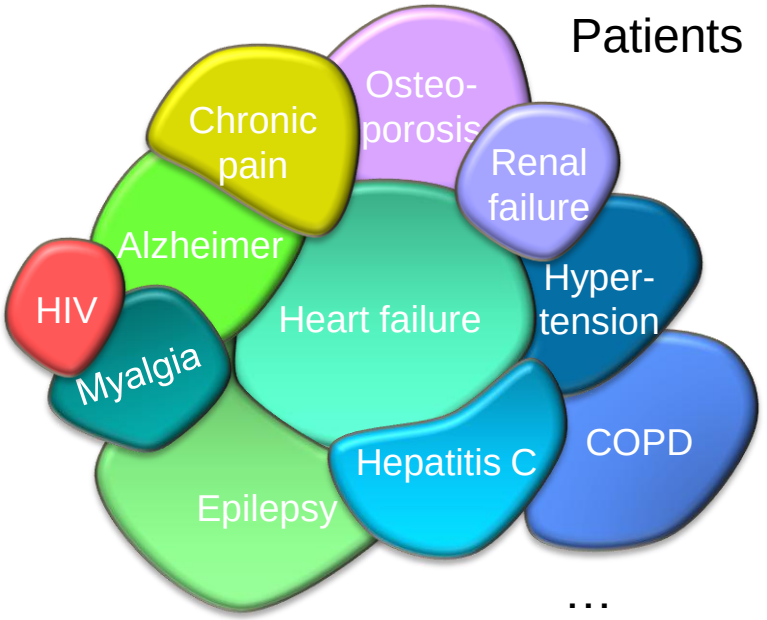
Can we transfer recruitment strategies from healthies to patients?

- Assuming that healthy and chronically ill populations are equally large…

Healthies



Patients



…only the healthy half can be universally adressed for early clinical studies!

Population Structures

In comparison to the healthy population

- patients present smaller populations, dependent on drug indication
- patients present distinct stages of progression excluding further subjects within the indication group
- on an average, patients are older
- no data on motivation for participation is available
  - Cave! No therapeutic benefit in early clinical trials!
- the mobility of subjects may be impaired, reducing the recruitment radius

It‘s all about the patients

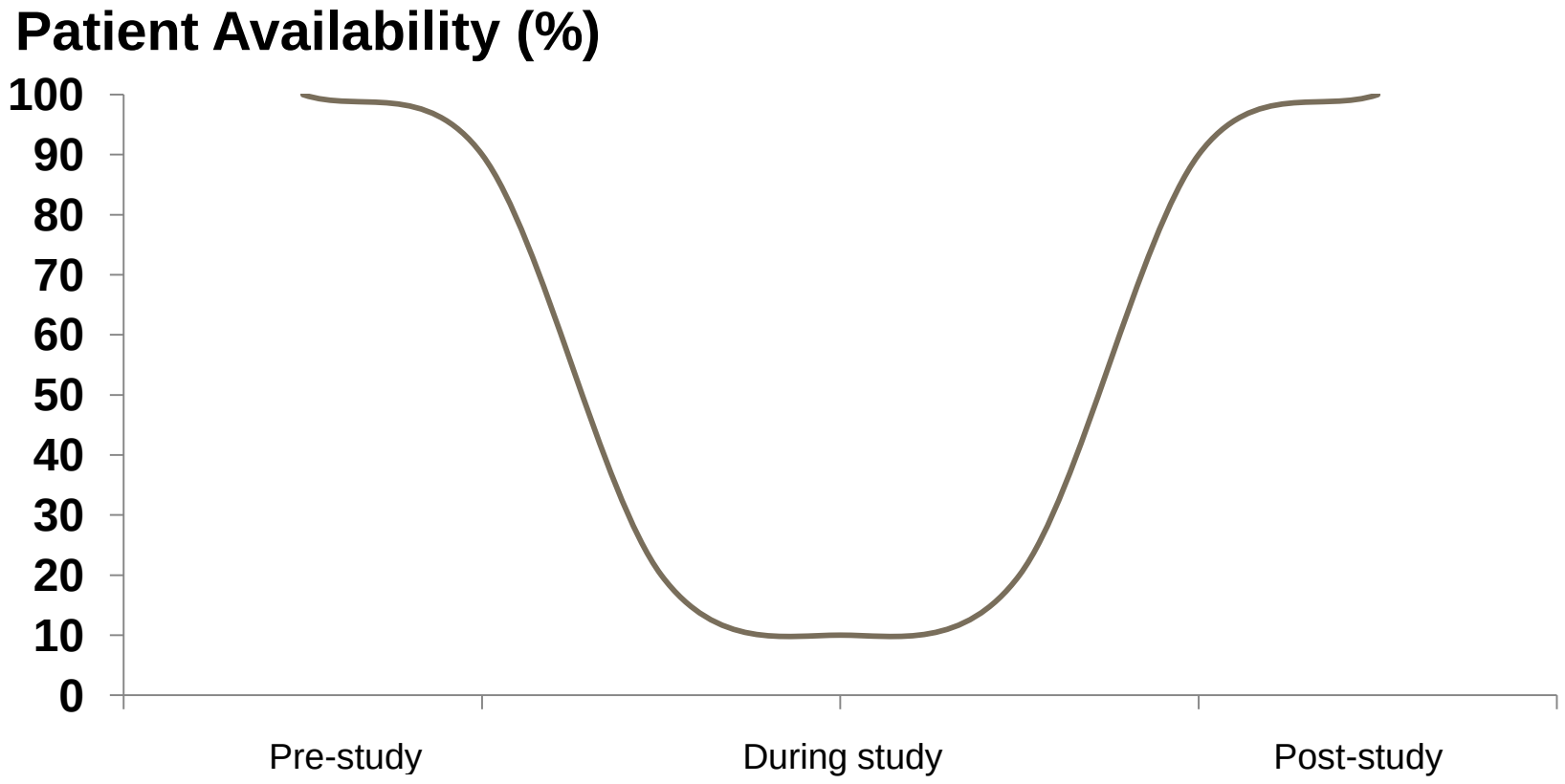
How do we have to recruit for Phase I patient trials?

Need for group-wise treatment in the resource-intense in-house phases

- Pool smaller groups of patients after defined collection periods
- Individual eligibility assessment by referring physician preferred
- Individual patient information and consent in the private practice

➢„Constant inflow“ of patients required for study success

Lasagna‘s Law



Reasons for underrecruitment

- Erroneous estimation of ratio between prevalent and incident cases and disease progression in prevalent cases
- Underestimation of inactive cases in the patient database
- Overestimation of willingness of patients to participate
- No focus on clinical trial recruitment during incident patient contact

➢A medical specialist can not be a professional recruiter!

➢More practitioners = accumulation of underrecruitment

Professional recruitment by CRO

- Adressing the general population by infomercials/advertorials covering some million people
- Include professional web-based services for further enhancement of trial-interested patients
- 12/5 (if not 24/7) hotline for interested patients to gather further information about clinical trials
- High standard pre-screening of candidates in telephone interviews
- Appointment management in close communication with the referring practitioner

Easing recruitment starts in trial design

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- Analysis of patient accessibility already during study design
- Simple designs convince more patients
- In-/Exclusion criteria in early clinical trials need thorough discussion: homogenous population vs. Recruitability
- Analysis and creation of motivational stimuli in case of lack of therapeutic benefit
  - Calculate incentives in close comparison to amount paid in HV trials
- Implementation of long enough periods between screening and treatment to collect groups for treatment start.
- Introduction of variable „synchronization“ periods to homogenize patients violating in-/exclusion criteria with temporary extent

Ethical implications

- Advertorial feature texts must be provided to IEC
- The pre-screening procedure and any information given to the patient during the first contact with the recruitment center should be throughly explained to IEC
- Advertorial and individual information by the practitioner should offensively adress any lack of therapeutic value
- Standard concomitant treatment of the target disease during prolonged periods between screening and study treatment and during study periods should be allowed
- Ample monetary allowance for patients no problem, if no therapeutic value of the trial for the patient

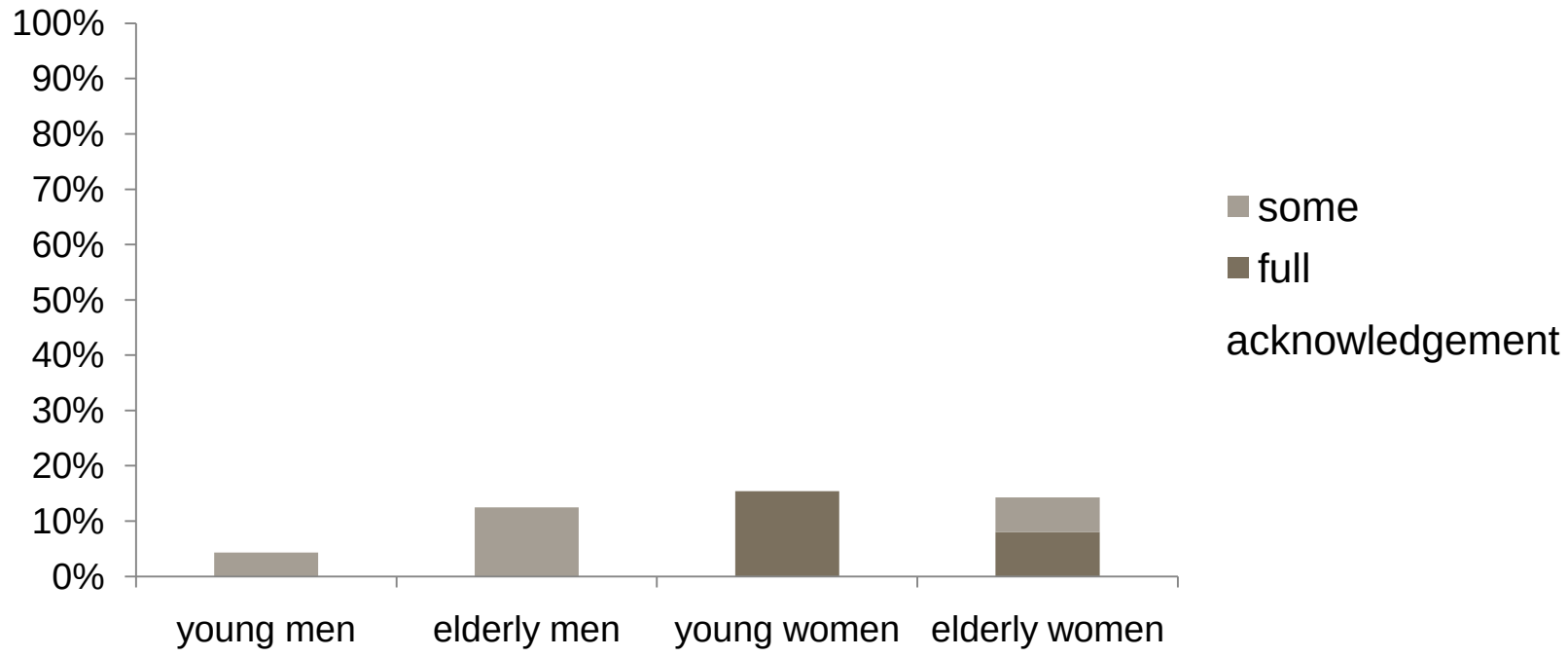
Good recruitment practice

- ***Design studies with patient recruitment in mind.***
  - Incorporating GRP from inception saves sponsors time and money while protecting the patient experience from initial inquiry through participation.
- ***Put patients first to benefit the entire medical research system.***
  - When you make optimized patient care a benefit to study participation, you improve patient, physician and public perceptions of clinical research.
- […]

J.F. Bachenheimer, B.A. Brescia, Reinventing Patient Recruitment (2007)

Improve public perception of clinical research

In healthy volunteers, how many experience acknowledgement by friends and relatives for their engagement (116 asked)?



Conclusions

Phase IIa/II studies with patients in a Phase I setting work

- In collaboration between practitioners and Phase I-CROs providing industry standards in patient trials
- In indications common enough to gather a critical mass of interested patients
- With studies custom-designed for swift recruitment in collaboration with experienced services
- Providing ample resources for supraregional feature-like advertisements, high standard recruitment services and proper allowances for trial participants