Registries: An alternative for clinical trials?

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Legal Aspects

EU Directive 2001/20/EC

Definitions

‘clinical trial’:
Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmaco-dynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy;

Legal Aspects

EU Directive 2001/20/EC

Definitions

‘non-interventional trial’:
A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. **No additional diagnostic or monitoring procedures shall be applied to the patients** and epidemiological methods shall be used for the analysis of collected data;

Anwendungsbeobachtung: Rechtliche Definition

§ 4 AMG

(23) Klinische Prüfung bei Menschen ist jede am Menschen durchgeführte Untersuchung, die dazu bestimmt ist, klinische oder pharmakologische Wirkungen von Arzneimitteln zu erforschen oder nachzuweisen oder Nebenwirkungen festzustellen oder die Resorption, die Verteilung, den Stoffwechsel oder die Ausscheidung zu untersuchen, mit dem Ziel, sich von der Unbedenklichkeit oder Wirksamkeit der Arzneimittel zu überzeugen.

Satz 1 gilt nicht für eine Untersuchung, die eine nichtinterventionelle Prüfung ist. Nichtinterventionelle Prüfung ist eine Untersuchung, in deren Rahmen Erkenntnisse aus der Behandlung von Personen mit Arzneimitteln gemäß den in der Zulassung festgelegten Angaben für seine Anwendung anhand epidemiologischer Methoden analysiert werden; dabei folgt die Behandlung einschließlich der Diagnose und Überwachung nicht einem vorab festgelegten Prüfplan, sondern ausschließlich der ärztlichen Praxis.

Non-interventional Studies

Different Definitions by Regulatory Authorities and Academic / Scientific Community

Regulatory Authorities

The term ‘interventional’ refers to any directions for treatment, diagnostics, follow-up schedules in the study plan etc.

➔ current practice

Non-interventional Studies

Academic / Medical scientific

Differentiates ‘interventional study’ and ‘observational study’ (e.g. cohort-, case control-study)

‘Intervention’ typically refers to directions for treatment only

➔ randomized clinical trial

Current absurdity

Drug regulation considers most observational studies like cohort or case control studies as ‘interventional trials’ as there are directions for diagnostics and follow-up in the research plan.

Registries

A registry is a file of data concerning all cases of a particular disease or exposure in a defined population such that the cases can be related to a population base

Non-interventional Studies (NIS) Registries

Research Objectives

- most often disease-specific, e.g. cancer registries
- epidemiology of disease
- health services research (Versorgungsforschung)
  - Quality of care, e.g. compliance with guidelines
  - Outcome quality
  - Utilisation of resources

Non-interventional Studies (NIS) Registries

In- and exclusion criteria for patients

- disease-specific
- representativity, routine care settings
- total population within a specified region and time frame

Caveat: No additional, registry-specific diagnostics or follow-up schedules

Non-interventional Studies (NIS) Registries

In- and exclusion criteria for participating centers

- Representativity
- routine care settings

Non-interventional Studies (NIS) Registries

Treatment / interventions

- no registry-specific directions for treatment at all stages of the diseases
- treatment (decisions) fall completely within current practice and / or the needs of the individual patients.

Non-interventional Studies (NIS) Registries

Design

- population-based cohort study
- physician-based
- no a priori hypotheses

Follow-up

- no registry-specific directions
  (→ drug-specific registries most often **no** NIS)

Non-interventional Studies (NIS) Registries

Sample size estimation

- depending to the objectives
- usual orientation:
  desired precision of the result
  → witdth of the 95%-CI

Non-interventional Studies (NIS) Registries

Statistical analysis

- descriptive
- either as a cross-sectional or cohort study
- sophisticated methods like Cox model etc feasible, too

Non-interventional Studies (NIS) Registries

Limitations

- Representativity often hard to achieve, non participation → selection bias
- most often no valid data re efficacy and safety (high quality registries may allow to assess effectiveness
- prospective registries may experience ethical problems → DSMB / DMC recommended

NIS Registries and ethics committees (German law)

- There is no legal requirement in Germany to consult an EC for a NIS
- In some German States professional regulations ask for consultation of an EC prior to the start of any epidemiologic study collecting personalized data
- anonymous data only → no requirement

Position of the ECs

- Current state of the art
- Research logic
- Choice of the most efficient design re validity of the results
- Good epidemiology practice (GEP) guidelines

Conclusions

- Registries are population-based cross-sectional or longitudinal observational data.
- High quality data require directions and uniform standards for diagnostics and follow-up.
- Registries with high quality data will usually not fulfill the legal criteria of a non-interventional study (NIS).
- Given the different objectives registries and clinical trials complement each others but should not be considered as alternatives.

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