How to interprete an Investigator's Brochure for meaningful Risk Assessment: View Point and Expectations of Ethics Committees

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CoI – Statement and Caveat

- There are no conflict of interests to declare.
- The views expressed here do not necessarily represent exactly those of the AKEK Germany.

Content

- **Definition, purpose of IBs and the tasks of RECs**
- **Current quality of IBs**
- **Conclusions**

IB – Definition and Purpose (ICH-GCP(R2) 7.1)

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial.

IB Nonclinical Studies - Efficacy Issues

- Relevance of the findings of the investigated therapeutic ...effects in humans;
- A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety.....

ICH-GCP(R2) 7.3.5

Inspection Order of Ethics Committees

- The scientific quality of the investigation
- The lawfulness
- the ethical acceptability
- the medical acceptability

German Medicinal Products Act - Section 40
General conditions for clinical trials

„The clinical trial of a medicinal product may only be conducted on human beings if and as long as:....

2. the foreseeable risks and inconveniences are medically justifiable, compared with the benefit for the person on whom the clinical trial is to be conducted (person concerned), and the anticipated significance of the medicinal product for medical science,...“

→ ***Preclinical data re efficacy and harm needed!***

Content of IBs typically reviewed by RECs

- Completeness re „relevant“data (ICH-GCP(R2) 7.1)
- Pharmacodynamic characteristics (preclinical and clinical)
- Safety findings (standard core battery: CNS, CV, repiratory, liver, kidneys)
- Toxicology findings (e.g. target organs)
- Calculation of the correct starting dose (e.g. NOAEL, MABEL, ATD)
- Summary of Data and Guidance for the investiga-tor

Noael: no observed adverse effect level; MABEL:minimal anticipated biological effect level; ATD: anticipated therapeutic dose range.

Quality of IBs

Sample: 109 IBs with 708 PCESs.

- Less than 5% of all PCESs described elements essential for reducing validity threats such as randomization, sample size calculation, and blinded outcome assessment.
- For most PCESs (89%), no reference to a published report was provided.
- Only 6% of all PCESs reported an outcome demonstrating no effect. For the majority of IBs (82%), all PCESs were described as reporting positive findings.

Quality of IBs - Conclusions

„The results show that most IBs for phase I/II studies did not allow evaluators to systematically appraise the strength of the supporting preclinical findings. The very rare reporting of PCESs that demonstrated no effect raises concerns about potential design or reporting biases. Poor PCES design and reporting thwart risk-benefit evaluation during ethical review of phase I/II studies.“

Wieschowski S et al. (2018) PLOS Biology 16(4)

Quality of IBs

Meta-analysis: 97 experiments involving 1,761 animals.

- Design elements to reduce internal validity threats were used rarely, with 66% reporting animal attrition and **none** reporting blinded outcome assessment or concealed allocation.
- Anticancer activity was typically tested in only a small number of model systems.
- Effect sizes were significantly smaller when sorafenib was tested against either a different active agent or combination arm. Trim and fill suggested a **37% overestimation** of effect sizes across all malignancies due to publication bias. Mattina J et al. (2016) Cancer Res 15;76

Quality of IBs - Conclusions

„In ***support of other reports***, we found that few preclinical cancer studies addressed important internal, construct, and external validity threats, limiting their clinical generalizability. Our findings reinforce the need to improve guidelines for the design and reporting of preclinical cancer studies.“

Mattina J et al. (2016) Cancer Res 15;76:4627-36

Preclinical Efficacy in Therapeutic Area Guidelines

Objective

To assess the guidance on PE in all available TAGs from EMA and FDA.

Key results

„A total of 114 EMA and 120 FDA TAGs were identified, covering 126 indications. Our core finding is that 75% of EMA TAGs and 58% from the FDA TAGs **do not offer any guidance on preclinical efficacy**. TAGs varied widely on the extent, nature and detail of guidance.“

Preclinical Efficacy in Therapeutic Area Guidelines

Conclusions and Implications:

„Guidance on preclinical efficacy in a consistent, comprehensive and explicit way that still allows for justified deviations is an important but neglected aspect of transparency for drug development. This transparency would help sponsors in designing preclinical studies and in negotiating more efficiently with regulators.“

Langhof H et al.: Br J Pharmacol 2018; 175:4229-38

Conclusions

- ✓ Comprehensive, good quality and up-to-date IBs are essential for a valid evaluation of the expectable benefit and harm of a clinical trial.
- ✓ At present such high-quality IBs seem to be, regarding preclinical data, rather the exception than the rule. There are insufficient data concerning the quality of the clinical data of IBs.
- ✓ As long as this situations persist IBs are of limited value for Ethics Committees.
- ✓ Ethics Committees should express their concerns about poor IBs more frankly.