Wie bindend ist bindend wirklich?

Die Rolle des Studienprotokolls …

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The trial/study protocol

Definition

- A document describing the
  - objective(s)
  - Design
  - Methodology
  - statistical considerations, and
  - organization of a trial.
- The central document

ICH (2016)

The trial/study protocol

Purpose

- Helps to do a study in a uniform and reproducible way
- Operating manual for investigators and other study personnel
  → a good protocol helps and is not a barrier
- Safeguard for study participants
- Defines the boundaries of the project (approval, consent, …)

Research

Human Research Act

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Art. 3a. Research means method-driven search for generalisable knowledge;

Protocol = ethics application?

A common missunderstanding

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Q: “Do you already have a study protocol or at least an outline?”

A: “Yes, I am currently working on the ethics application!”

Protocol = ethics application?

A common missunderstanding

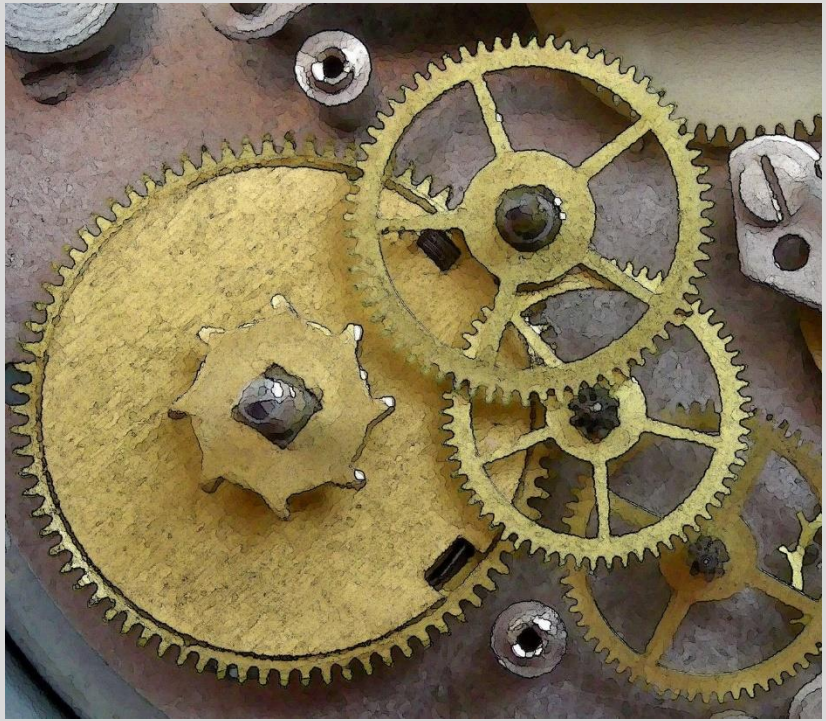
– People often talk about the protocol as being “the ethics application”

→ Although the protocol has to be submitted to the ethics committee and despite the fact that study protocols should usually be written using the Swissethics protocol templates, it has **nothing** to do with the **ethics** application **per se**.

Required level of detail

How precise/detailed should it be?

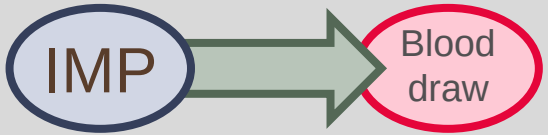
- Depends …
  - See purpose → uniformity, reproducibility, etc.
  - Different between studies and disciplines, example
    - Blood pressure measurement in a hypertension trial versus a physiotherapy trial
- Changing over time (old versus new protocols)

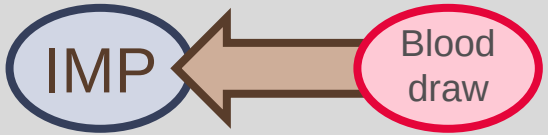


Finding the right balance

Sometimes difficult …

- In order to simplify for the sites, the study procedures are clearly described in the protocol …
- Day 1
  The blood draw for t=0 should be performed as soon as possible after IMP administration during Day 1.
- Week 4
  The second IMP administration for each patient will be performed during the scheduled Week 4 visit, after completion of vital signs and blood draw procedures.





Finding the right balance

Sometimes difficult …

- The order of IMP injection and blood draw had no significance, no impact on study outcomes nor patient safety.
- The sponsor informed the sites that they can perform these operations in the order they prefer.

→ The protocol should be followed, and any significant changes should be submitted to the EC and the regulatory authorities for approval before implementation.

→ In case the change is considered non-significant, the new protocol version should nevertheless be submitted as soon as possible to the regulatory authorities and with the next amendment or, at the latest, with the next annual safety report to the EC.

The swissethics template

Common pitfalls

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2.7 Patient Information and Informed Consent

… The consent form must also be signed and dated by the investigator (or his designee) at the same time as the participant sign and it will be retained as part of the study records.

10.1 Drug studies

… During the entire duration of the study, all adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and case report forms (CRF).

Detailed/precise but not necessarily rigid

Quality-By-Design

≠

The eligibility criteria

How strict is strict …

– Clear rules that should be applied without interpretation or subjective evaluation

– A **non-eligible** patient should **never** be included….

…. and an **eligible** patient should **always** be included

– In the beginning of a study, it is sometimes (often?) realized that inclusion and exclusion criteria are too narrow

– Changes need to be implemented in the protocol before relaxing the inclusion and exclusion criteria applied for patient enrolment

→ No individual(ized) decision-making

How strict is strict in practice?

Some examples – I

- Exclusion criteria
  - Concentrations of serum IgG below 5.0 mg/mL and of IgM below 0.40 mg/mL
- Potential participant: IgM was 0.340
- Investigator stated in the eligibility check-list that “value not clinically significant” and included the patient …

How strict is strict in practice?

Some examples – II

- Exclusion criteria
  - Any of the following
    - nystagmus
    - dissociated vertical deviation
    - inferior oblique muscle overaction
    - superior oblique muscle overaction
- The exclusion criteria were defined to exclude patients with congenital esotropia. Unfortunately, the criteria also apply to other patient groups, that are potentially eligible for the study.
- The eligibility criteria were adjusted and submitted to the ethics committee and Swissmedic

How strict is strict in practice?

Some examples – III

- Visit schedule, for example follow-up visits (days after randomization)
  - 28 and 90 days
  - 28 +/-2 and 90 +/-10 days
  - 26-30 and 80-100 days (if time window was missed (protocol deviation), still try to get assessments as soon as possible and record)

Life voting

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Main issue (root cause) in practice

Physician versus investigator (researcher)

Take home message

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- ☞ Clinical study ≠ clinical practice!
- ☞ Follow the protocol – **strictly**
- ☞ If not possible
  - ↳ External sponsor: Contact sponsor
  - ↳ You are the sponsor: Amend the protocol

Next CTU Lecture

http://www.ctu.unibe.ch/training_courses/ctu_lectures/index_eng.html

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- Do 16.05.2019, 12:45-13:30
- ZMK
  André Schröder Auditorium

Thank you!

for your attention …

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References

- Brody & Miller (2003): Kennedy Institute of Ethics Journal; 13: 329-46.
- ICH (2016): International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Guideline for Good Clinical Practice E6(R2).

Pictures

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