Workshop, 12.3.2015

Clinical trials of medical devices

Frequent problems seen in category C clinical investigation plans

Specificities of Standard ISO 14155 (GCP for medical devices)

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clinicaltrials.devices@swissmedic.ch

Topics for discussion

1. Introduction
2. Pilot studies and pivotal studies
3. Vulnerable patients (emergency situations, minors, patients unable to understand or decide, pregnancy)
4. Patients lost to follow-up
5. Elective invasive interventions and informed consent
6. Specificities of SAE reporting for devices
7. Monitoring, archiving
8. Cooperation between hospitals, universities, practicing doctors, start-ups and other companies
9. CRF

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1. Introduction

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1. Introduction

- Economical value of the MedTech sector is comparable to the pharmaceuticals sector
- Proportion of small and medium enterprises >90 %
- Lifecycle of high-tech medical devices as short as 2 years
- 105 pre-market clinical trials of medical devices carried out in Switzerland right now

1. Introduction

New since 1.1.2014

- Tasks of Swissmedic described in Art. 54 HMG / TPA
- Tasks are not the same for clinical trials of medicinal products and medical devices

Art. 54 HMG /TPA

1 **Klinische Versuche mit Heilmitteln bedürfen vor ihrer Durchführung einer Bewilligung des Instituts.**

2 **Ausgenommen** von der Bewilligungspflicht sind klinische Versuche mit:

a. zugelassenen Arzneimitteln, die im Rahmen der zugelassenen Anwendungsbedingungen verabreicht werden;
b. konformen Medizinprodukten, die innerhalb der in der Konformitätsbewertung vorgesehenen Zweckbestimmung angewendet werden.

3 {…}

4 **Im Rahmen des Bewilligungsverfahrens prüft das Institut, ob**:

a. die Arzneimittel die Anforderungen der Guten Herstellungspraxis sowie diejenigen an die Arzneimittelsicherheit erfüllen; oder
b. **die Medizinprodukte die Anforderungen nach Artikel 45 erfüllen, die Produkterisiken im klinischen Versuch berücksichtigt werden sowie ob die Produkteangaben dem wissenschaftlichen Stand entsprechen und im Prüfplan korrekt abgebildet wurden.**

5 {…}

1. Introduction

Status as of 1.2.2015

- **105** active pre-market clinical trials of devices (approved, not yet closed)

- **10** clinical trials undergoing approval procedure

1. Introduction

	Pharmaceuticals (ICH-Guidelines)	Medical devices (EN ISO 14155:2011 and others)
Standardisation of clinical development phases	Highly standardised (phase I, II, III)	Not standardised, it depends…. Review of CIP is paramount
Methods for pivotal trials	Highly standardised (double blind, randomised, controlled)	Not standardised, it depends…. Review of CIP is paramount
Irreversible effects on study subjects	Rare	Very common. Review of CIP is paramount. Challenges affecting informed consent, vulnerable patients, many of the study procedures of the CIP.
Research in vulnerable subjects	Easier to detect	Good checklist needed
Size of companies involved in research	Mostly large	Large to very small, many start ups
Know-how	Easier to build up	More difficult to build up

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2. Pilot studies and pivotal studies

2. Pilot studies and pivotal studies

Is a pilot study necessary before large numbers of subjects can be recruited?

- Situation is simple for most pharmaceuticals:

  Yes (phase I, II, III studies)

- Situation for medical devices:

  It depends…..

2. Pilot studies and pivotal studies

•Pharmaceuticals: phase I, II, III studies

- If you change the molecule, it becomes a New Active Substance
- Full battery of preclinical tests needed, standardised clinical development with phase I, II, III clinical trials
- There are but few exceptions to this rule

2. Pilot studies and pivotal studies

Is a pilot study necessary before large numbers of subjects can be recruited?

•Situation for medical devices: It depends…..

- Mostly incremental developments.
- Differences and innovation often affect few elements or aspects only.
- Some devices or elements have negligible interactions with the body and their design induces no relevant clinical risks during a trial.
- Expected risks are usually described, but documentation is not always clear enough: What aspects are identical to conforming products, slightly different, highly innovative?

2. Pilot studies and pivotal studies

Is a pilot study necessary bef… …ects can be recruited?

- You are the reviewer
  - is the documentation clear enough?
  - Do you think the differences and innovations can turn out to be deleterious to the study subjects (usability, efficacy, long term safety, others)?
  - Is it admissible to go right away for 120 patients and to bypass EC and CA review of the results of pilot phases?

2. Pilot studies and pivotal studies

Example of what you can see in studies (Gaussian distribution)

Chance of observing at least one event	80%	80%	80%
Actual probability of the event	10%	5%	1%
n	15	31	161

2. Pilot studies and pivotal studies

Is a pilot study necessary before large numbers of subjects can be recruited?

Examples:

1) In an implantable pacemaker-defibrillator, the battery was improved (same size and weight, better longevity), the rest of the device remains unchanged.

2) The catheter system for the implantation of a coronary stent was improved, the stent remains unchanged.

2. Pilot studies and pivotal studies

Is a pilot study necessary before large numbers of subjects can be recruited?

Whenever there is a stand alone pivotal study (*) AND significant risks, the reviewer needs to evaluate the situation carefully

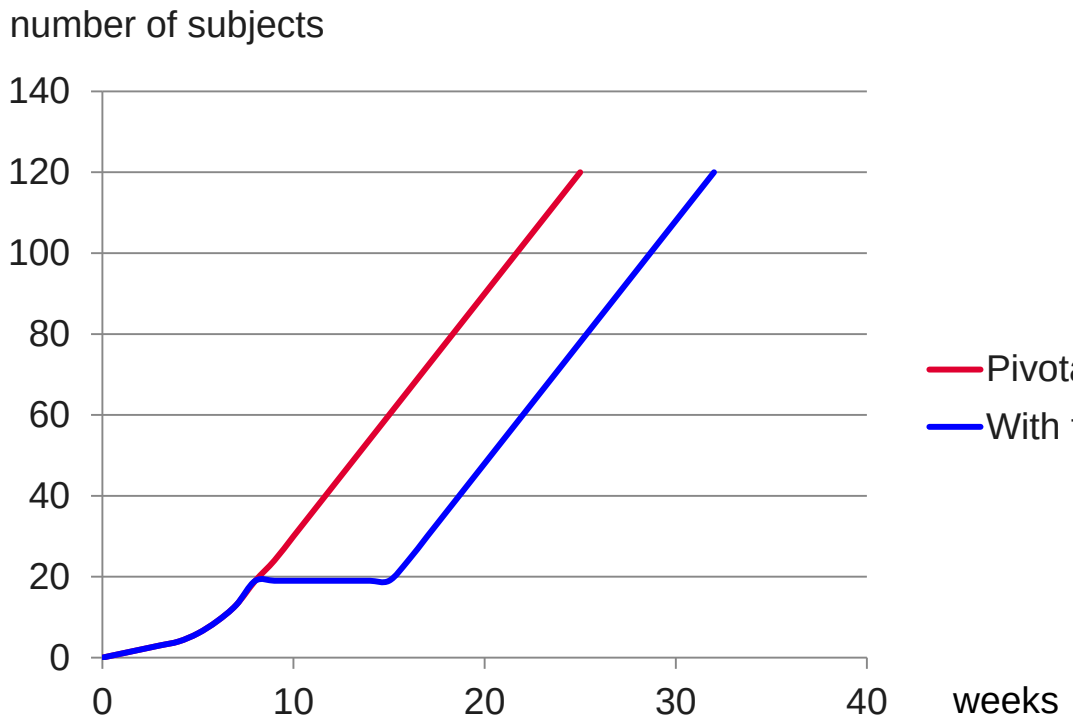
(*) in this context, stand alone means

- *without results of previous pilot studies*
- *nor built in first-in-man cohort, interim analysis, EC and CE review of first-in-man results before recruitment is extended*

2. Pilot studies and pivotal studies

Is a pilot study necessary before large numbers of subjects can be recruited?

How many subjects are put at risk or exposed unnecessarily?



2. Pilot studies and pivotal studies

Science in pivotal studies

- Situation is simple for most pharmaceuticals:
  Double blind randomised controlled

- Situation for medical devices: It depends…..

2. Pilot studies and pivotal studies

Science in pivotal studies for medical devices

- European Requirements (Annex 10 of directive 93/42/EEC):

> *"Clinical investigations must be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer's claims for the device; these investigations must include an adequate number of observations to guarantee the scientific validity of the conclusions."*

Sound methodology also required for devices…!

2. Pilot studies and pivotal studies

Control arm necessary? Watch out for the following situations:

- Self-limiting diseases, fluctuating or subjective symptoms, regression to the mean.
- Bias due to concomitant therapies, environmental effects.
- Device factors, user skills, patient factors all having intricate influence on results that is impossible to sort out.
- Hypotheses or pass/fail criteria based on historic controls not comparable to the study population or study situation.
- Unknown mechanisms of action.

Biased clinical trials are unethical and illegal.
Useless or harmful interventions would seem beneficial.
Validity of trial results can be rejected later on by regulators and inspectors. Do not hesitate to correct protocols.

2. Pilot studies and pivotal studies

Science in pivotal studies for medical devices

- The design depends on characteristics of devices and diseases:
  - Control arm: Some trials require a control arm, not all.
  - Randomisation: When there is a control arm, randomisation is necessary.
  - Blinding: When a randomised controlled trial is to be carried out, blinding might be possible for certain devices and should be done as far as possible (Blinded users? Blinded patients? Investigators who evaluate symptoms or function? Core labs?) > to be checked

2. Pilot studies and pivotal studies

Science in pivotal studies for medical devices

- Statistics, required contents include

- objectives
- claims and intended device performance to be verified, risks and anticipated adverse device effects to be assessed
- clinically relevant endpoints, hypotheses
- statistical design, level of significance, power
- expected drop-out rates
- sample size calculation
- pass/fail criteria to be applied to the results, etc.

(Ref.: EN ISO 14155:2011, A.5 to A.7)

For pivotal studies professional statistical planning is necessary!

3. Vulnerable patients

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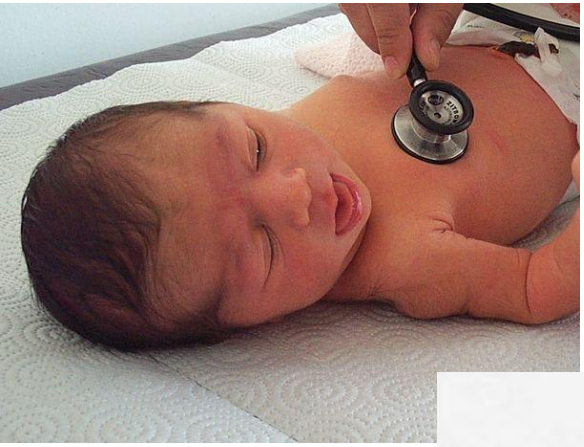

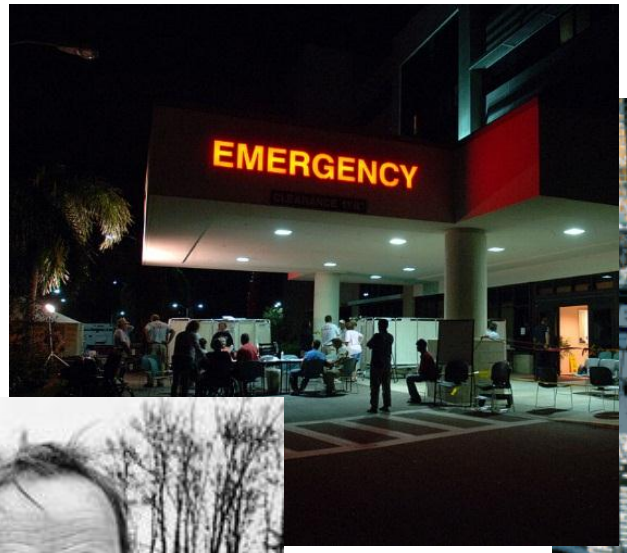

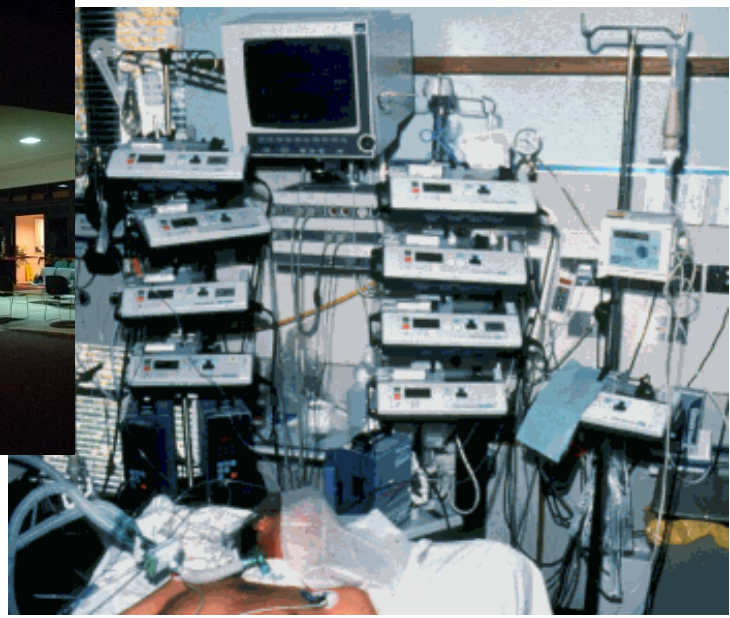

If not excluded with inclusion and exclusion criteria, we are in it…

3. Vulnerable patients

- Admissible?

„Ein Forschungsprojekt mit besonders verletzbaren Personen darf nur durchgeführt werden, wenn gleichwertige Erkenntnisse anders nicht gewonnen werden können.“
(+ andere Bestimmungen)

„Un projet de recherche ne peut être réalisé sur des personnes que si des résultats équivalents ne peuvent pas être obtenus autrement.“
(+ autres dispositions)

(Ref.: Article 11.2 HFG/HRA)

3. Vulnerable patients

- Documents OK?
  - Are reasons for involving vulnerable subjects described?
  - Is the paperwork available and correct?
    - **Emergency situation**: Texts and forms for the patients, the independent doctors, for consecutive information and consent to be used as soon as possible. Description of the procedure (who will carry out which step, when, with what document?)
    - **Minors**: Information and consent forms for children, adolescents, and their parents.
    - **Adults not legally competent / unable to evaluate the situation**: Information and consent forms for the patients, and for their legal representatives.

4. Patients lost to follow-up

4. Patients lost to follow-up

Mortality endpoints, endpoints causing disability

- CIP:
  - If trial subject can no longer be contacted, rapid contacts with other persons or institutions, clarification of state of health.
  - If death or SAE cannot be established, sensitivity analyses should usually be foreseen, described in the protocol, disclosed in final reports and publications.
  - Monitoring shall include surveillance on subjects lost to follow-up, including attempts made to contact subjects and third parties.
- Consent form: Must contain agreement that the investigator may retrieve health data from the family doctor and/or other listed persons and institutions (not covered by the standard template).

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5. Elective invasive interventions and informed consent

5. Elective invasive procedures

Reflection period: How much is enough?

- Publications of cases of the federal court concerning clinical routine (www.bger.ch)
- For example case „4P.265/2002“
- Important in research projects involving
  - implants
  - permanent modification to bodily parts
  - high-risk, invasive examinations

5. Elective invasive procedures

Reflection period: How much is enough?

- Review of CIP:
  Recurrent issues, review of texts but also of tables showing the timing of study procedures is neccesary.

- Inacceptable study procedures:
  - Explanations regarding a trial and obtaining the written consent during the same visit.
  - Explanations regarding a trial and study specific baseline procedures during the same visit (e.g. additional x-ray for the decision if patient is a suitable candidate for the trial)
  - Explanations regarding a trial after being hospitalised for an elective procedure.

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6. Specificities of SAE reporting for devices

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Definition of Serious Adverse Event (SAE):
Important differences between…

ICH-GCP (medicinal products)	**MEDDEV 2.7/3 (medical devices)**
Any untoward medical occurrence that at any dose:	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device that: NOTE 1: This includes events related to the investigational device or the comparator. NOTE 2: This includes events related to the procedures involved (any procedure in the clinical investigation plan). NOTE 3: For users or other persons this is restricted to events related to the investigational medical device.
- results in death,	a) led to a death,

6. Specificities of SAE reporting for devices

Continuation…

ICH-GCP (medicinal product)	**MEDDEV 2.7/3 (medical devices)**
- is life-threatening,	b) led to a serious deterioration in health that either: 1) resulted in a life-threatening illness or injury, or 2) resulted in a permanent impairment of a body structure or a body function, or
- requires inpatient hospitalization or prolongation of existing hospitalization, or	3) required in-patient hospitalization or prolongation of existing hospitalization, or
	4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

6. Specificities of SAE reporting for devices

Continuation…

ICH-GCP (medicinal product)	MEDDEV 2.7/3 (medical devices)
- is a congenital anomaly/birth defect	c) led to fetal distress, fetal death or a congenital abnormality or birth defect.
	NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system. NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

6. Specificities of SAE reporting for devices

Serious Adverse Event (SAE) continuation…

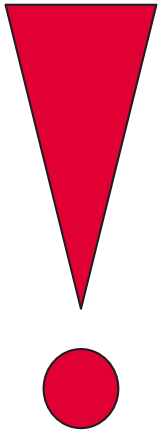
Swiss reporting requirements to EC and CA are more extensive for devices than for pharmaceuticals

- reporting within 7 days
- of all SAE that could be related to devices or procedures
- including expected SAE

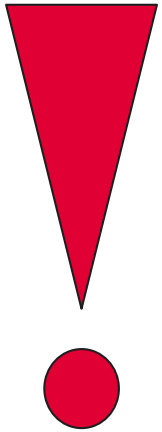
(Reporting requirements are more extensive in the EU, all SAE must be reported. Changes foreseen with revision of the European regulatory framework for medical devices)

6. Specificities of SAE reporting for devices

Conclusion



- In pre-market clinical trials of medical devices, never accept study procedures based on pharmaceuticals:
  - ICH-GCP definition of SAE is inacceptable
  - reporting system is inacceptable



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7. Monitoring, archiving

7. Monitoring, archiving

- Monitoring requirements for devices are highly detailed.
  Do not rely on ICH-CGP provisions,
  read EN ISO 14155 instead.

- CIP:
  - Monitoring must be described
  - Qualitative descriptions are insufficient.
  - What percentage of source data verification?

7. Monitoring, archiving

- Be aware of archiving duties
  Many applications have to be corrected

implanted medical devices	**15 years**
medicinal products non-implanted medical devices	**10 years**

Never two years (USA)

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8. Cooperation between hospitals, universities, practicing doctors, start-ups and other companies

8. Cooperation

Lots of problems in case of unclear roles

- Have the roles been clearly attributed?
- Who is the sponsor?
  - There can be only one (we have never seen an acceptable solution where QMS deficiencies have been solved)
  - The sponsor must be insured
  - Must also organise monitoring, the monitor cannot be one of the investigators (nor staff of investigators)
- Who is the manufacturer?
  - There can be only one
  - If manufacturer is not the sponsor, must have a contract with the sponsor (for all devices that are not available on the market, or when manufacturer is involved in the clinical study).

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9. CRF

9. CRF

A thorough check of the CRF regarding congruency with the protocol is necessary, especially for

- Inclusion and exclusion criteria
- Study procedures at each visit
- Patient questionnaires in local language(s)
- AE- and SAE-forms with correct definitions and reporting procedures
- Anonymisation
  (no patient names, no combination of initials and date of birth).

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Additional information available in the following information sheet:

BW101_50_002e_MB

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Thank you for attending