Clinical research in Portugal: meet the players

Principal investigator: competencies and responsibilities

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- Clinical trials are fundamental to the development of innovative, investigational products such as drugs or high-risk medical devices.

- Many products are found to be safe and effective in bench testing, *in vitro* testing or animal studies, but fail to demonstrate the same effect in humans.[1,2]

- These investigational products **must be proven safe and effective in a clinical study in humans** before use in the general population.

1- Canada trials. (2008, April 26.) *What is clinical research?* Retrieved July 13, 2012, http://www.canadatrials.com/AboutClinicalResearch.php.
2- People for the Ethical Treatment of Animals. (n.d.). *Animal Experiments: Overview*. Retrieved September 24, 2012, from http://www.peta.org/issues/animals-used-for-experimentation/animal-experiments-overview.aspx.

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Clinical Trial/Study

- Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.

ICH Topic E 6 (R1)
Guideline for Good Clinical Practice
July 2002
CPMP/ICH/135/95

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Clinical trials and Good Clinical Practice (GCP)

- **Good clinical practice (GCP) is an international ethical and scientific quality standard** for designing, conducting, monitoring, auditing, recording, analyses, and reporting **clinical trials** that involve the participation of human subjects.[1]

- Provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentially of trial subjects are protected.

- Regardless of whether a clinical trial is a large, multi-centre study in patients or a small clinical pharmacological study in healthy subjects, the relevant GCP standard should be followed by the **sponsoring company** of the healthcare product, **the investigators**, the **ethics committees** and any **clinical research organizations**

1- Tobin, J.J. & Walsh, G. (2008). Chapter 5. Clinical trial. In *Medical product regulatory affairs. Pharmaceuticals, diagnostics, medical devices*. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA.

International Conference on Harmonisation (ICH) GCP Guideline

- "**Objective:** to provide a unified standard for the EU, Japan and the US to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

- The guideline was developed with consideration of the current good clinical practices of the EU, Japan, and the US, as well as those of Australia, Canada, the Nordic countries and the WHO

- The guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities

- **The principles established in the guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects."**

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Good clinical practice and the ICH

- Prior to the GCP guidance document developed by ICH, different jurisdictions had different guidelines relating to the conduct of clinical trials.

- With the introduction of ICH GCP, the conduct of clinical trials globally has become more uniform and practicable. **Today, the implementation of ICH good clinical practice in most jurisdictions is reasonably similar and the vast majority of the regulations are the same.**

- **Healthcare product developers should therefore work to ICH in the context of local regulations.**

Thirteen core principles of ICH Good Clinical Practice

1. **Ethical principles: declaration of Helsinki**
2. **Favourable benefit(s) vs. Risk(s)**
   - A clinical trial should be initiated and continued only if the anticipated benefits justify the risks.
3. **Subject's rights**
   - The rights, safety and well-being of the trial subjects override the interests of science and society.
4. **Adequate supporting data**
   - The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. **Scientifically sound protocol**
6. **Independent ethics committee oversight**

Thirteen core principles of ICH Good Clinical Practice

7. **Medical care by qualified investigator**
   - The medical care given to subjects, and the medical decisions made on their behalf, should always be the responsibility of a qualified physician ..
8. **Qualified personnel**
   - Each individual involved in conducting a clinical trial should be qualified by education, training and experience to do their respective task(s).
9. **Informed consent**
   - Freely-given informed consent should be obtained from every subject prior to participation in the clinical trial.
10. **Record-keeping**
11. **Subject confidentiality**
12. **GMP manufacturing of the investigational product**
13. **Quality assurance & monitoring**

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Investigator (PI)

A person responsible for the conduct of the clinical trial at a trial site.

If a trial is conducted by a team, the investigator is the responsible leader of the team and may be called the principal investigator (PI)

Subinvestigator

- **Any individual member of the clinical trial team designated and supervised by the PI at a trial site** to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

PI responsibilities

Qualifications and Agreements

The investigator(s) should

- be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, (…) and should provide evidence of such qualifications through up-to-date CV and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies)
- comply with, GCP and the applicable regulatory requirements
- permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies)
- maintain a list of appropriately qualified persons to whom has delegated significant trial-related duties

Protocol No.:	Centre No.:

- PRINCIPAL INVESTIGATOR -

Title, First Name and Surname:	Work address:	
Signature:	Telephone:	Initials:

- PERSONNEL [1] INVOLVED IN THE STUDY IN THIS CENTRE, UNDER PRINCIPAL INVESTIGATOR'S RESPONSIBILITY -

Function	Name	Tasks delegated by the principal investigator under his/her responsibility [2, 3]	Dates of participation in the study		Signature [4]	Initials	Certification by principal investigator / Signature
			Start	End			
Principal Investigator							

CONFIDENTIAL

[1] *Indicate the people to whom the principal investigator delegates under his/her responsibility a part of the study follow-up (study nurse, co-investigator…)*

[2] *See list attached*

[3] *For principal investigator, tasks actually performed by the principal investigator*

[4] *Signature means "I hereby certify that I have been informed of documents confidentiality as well as read and understood all study documentation that apply to my task(s) in the study"*

PI responsibilities

Adequate Resources

The PI should

- be able to demonstrate (e.g., based on retrospective data) **a potential for recruiting the required number of suitable subjects within the agreed recruitment period**
- have **sufficient time to properly conduct and complete the trial within the agreed trial period**
- have available an **adequate number of qualified staff and adequate facilities for the foreseen duration of the trial** to conduct the trial properly and safely
- **ensure that all persons assisting with the trial are adequately informed** about the protocol, the investigational product(s), and their trial-related duties and functions

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PI responsibilities

Communication with IRB*/IEC**

The PI should:

- **Before initiating a trial, have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol**, written informed consent form, consent form updates, subject recruitment procedures, and any other written information to be provided to subjects

- Provide a current copy of the Investigator´s Brochure (and the updates during the trial, plus all documents subject to review)

***Institutional Review Board**
**** Independent Ethics Committee**

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PI responsibilities

Compliance with Protocol

The PI should not

- Implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, **except where necessary to eliminate an immediate hazard(s) to trial subjects** (…)

- **Any deviation from the approved protocol must be documented and explained** (the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s)) **and should be submitted to the IRB/IEC, to the sponsor** and, if required, to the regulatory authority(ies)

PI responsibilities

Investigational products

The Investigator/other person designated by the investigator, should

- Maintain records of the product´s delivery to the trial site, the inventory at the site, the use by each subject , and the return to the sponsor or alternative disposition of unused product(s)
- Ensure that investigational products are stored as specified by the sponsor and **used only in accordance with the approved protocol**
- **Explain the correct use of investigational products to each subject** and check, at intervals appropriate for the trial, that each subject is following the instructions properly

PI responsibilities

Randomization Procedures and Unblinding

The investigator should follow the trial´s randomization procedures, if any, and should ensure that the code is broken only in accordance to protocol

If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to serious AE) of the investigational product

PI responsibilities

Medical Care of Trial Subjects

A qualified physician (the PI or a subinvestigator for the trial), should be responsible for all trial-related medical decisions

- **During and following a subject´s participation in a trial**, the investigator/institution **should ensure that adequate medical care is provided to a subject for any adverse events related to the trial**

- **It is recommended that the investigator inform the subject´s primary physician about the subject´s participation in the trial** if the subject has a primary physician and if the subject agrees to the primary physician being informed

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PI responsibilities

INFORMED CONSENT OF TRIAL SUBJECTS

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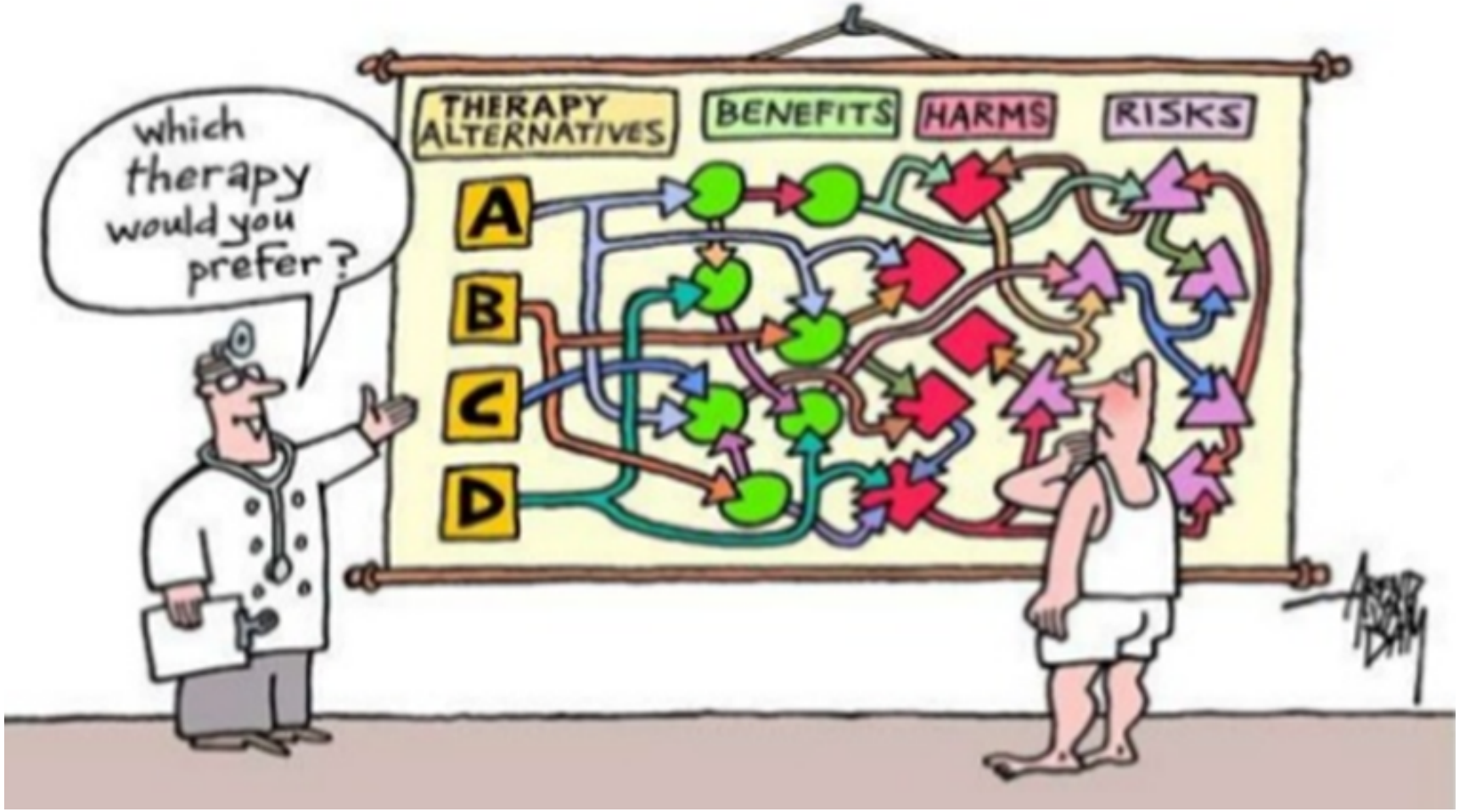
PI responsibilities



? Informed consent ?

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PI responsibilities

Informed consent

The PI or a subinvestigator for the trial, should fully inform the subject,* of all pertinent aspects of the trial including the written information and the approval/favourable opinion by the IRB/IEC

- **The language used about the trial**, including the written informed consent form, **should be as non-technical as practical and should be understandable to the subject***

- **Provide ample time and opportunity to inquire about details of the trial and to decide whether or not to participate. All the questions should be answered to the satisfaction of the subject***

*** Or , if the subject is unable to provide informed consent, the subject´s legally acceptable representative**

PI responsibilities

Records and reports

- **The Investigator should ensure the accuracy, completeness, legibility, and t** …id in all requ…

- **Any …** …(this appli…

- **The i… Docu…** …its

- Upon… …ority, the inves… **requ…**

*Those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced

PI responsibilities

Progress reports

- **The Investigator should**

  Submit written summaries of the trial status to the IRB/IEC **annually,** or more frequently, if requested

  Provide written reports to the sponsor, the IRB/IEC and, where applicable, the institution **on any changes** significantly affecting the conduct of the trial, and/or increasing the risk to subjects

PI responsibilities

SAFETY REPORTING

All SAEs should be reported immediately to the sponsor (and be followed by detailed, written reports)

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PI responsibilities

Premature termination or suspension of a Trial

- If the trial is prematurely terminated or suspended for any reason, **the investigator/institution should**
  - promptly inform the trial subjects
  - Assure appropriate therapy and follow-up for the subjects

Final report (upon completion of the trial)

- The investigator should inform the institution and provide the IRB/IEC with a summary of the trial outcome

"There are 3 actions of a drug:

the one we want,

the one you don't want, &

the one you don't know about"

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