INVESTIGATIONAL PRODUCTS

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GCP workshop on Clinical Trials
FERCSL- October 8-9, 2015

1. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. World Health Organization. WHO Technical Report Series, No. 850, 1995, Annex 3
2. Note for guidance on Good Clinical Practice (CPMP/ICH/135/95). ICH Topic E 6 (R1). July 2002
3. International ethical guidleliens for biomedical research invloving human subjects. CIOMS and WHO publication: 2002
4. Eurpean commission Directive: 2005/28/EC. 8 April 2005
5. European commission Directive: 2002/20/EC
6. European commission: Enterprise and Industry Directorate- General. Consumer goods. Pharmaceuticals
7. ICH harmonized tripartite guideline . Guideline for GCP: Topic E6(R1)
8. REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
9. Handbook for good clinical research practice (GCP). World Health Organization. 2002
10. Pocock S J. Introduction: The rationale of clinical trials. IN: Clinical Trials. A practical approach. Singapore: John Wiley & Sons; 1989

Clinical Trial

"A clinical trial is any research study that **prospectively assigns human participants or groups of humans to one or more health-related interventions** to evaluate the effects on health outcomes.

Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, devices, behavioral treatments, process of care changes".

WHO-ICTR definition

Clinical Trial – Definition 2

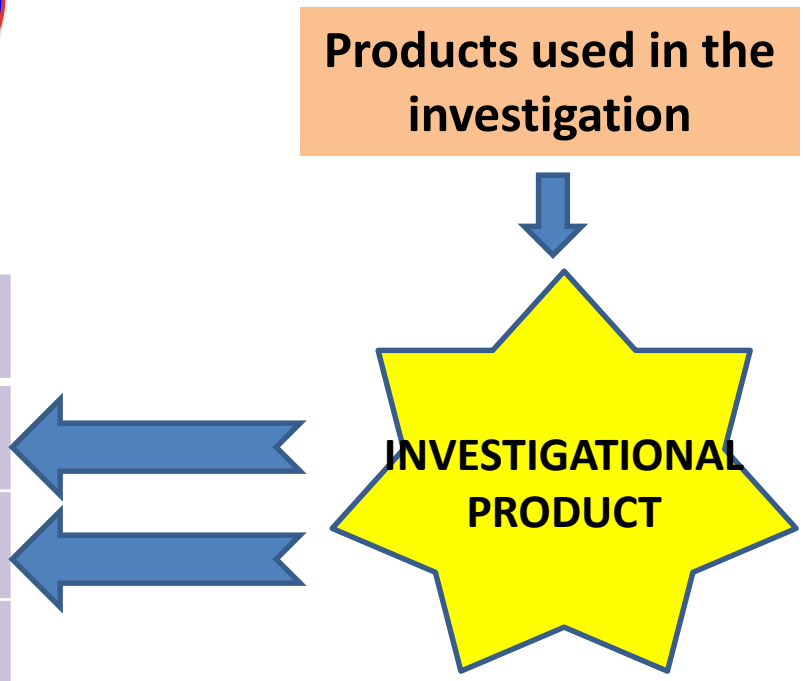
- "Any form of carefully planned, and ethically designed experiment with the aim of answering some precisely framed question which involves patients and is designed to elucidate the most appropriate treatment of future patients with a given medical condition"

Pocock S J. Introduction: The rationale of clinical trials. IN: Clinical Trials. A practical approach. Singapore: John Wiley & Sons; 1989

For any clinical question……

PICO

P	PARTICIPANTS
I	INTERVENTION
C	CONTROL
O	OUTCOME



Sackett D, Richardson WS, Rosenburg W, Haynes RB. How to practice and teach evidence based medicine. 2nd ed. Churchill Livingstone; 1997.

PICO- FINER

F	FEASIBLE
I	INTERESTING
N	NOVEL
E	ETHICAL
R	RELEVANT

Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing clinical research. 3rd ed. Lippincott Williams and Wilkins; 2007

As per WHO-ICTR definition…..

- Interventions can be:
  - Medicinal (pharmaceutical)
  - Non-medicinal: Devices, cosmetic, nutritional supplements, exercise programmes, vaccines, health education programmes, etc
- Hence investigational products (products used in the investigation) too can be:
  - Medicinal
  - Non-medicinal

INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

Medicinal Product

(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

European Commission: Article 1.1 of Directive 2004/27/EC

Clinical trial

- Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic 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 to 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.

European commission: Article 2 (c) of Directive 2001/20/EC

Medicinal Products in a clinical trial

1. Investigational

2. Non-investigational

http://ec.europa.eu/health/files/pharmacos/docs/doc2006/07_2006/def_imp_2006_07_27_en.pdf

Investigational Medicinal Product

1. Within the definition of a medicinal product
2. Within the definition of a clinical trial (objective – clinical trial)
3. Intended use of the product should be test/ active comparator/ placebo

http://ec.europa.eu/health/files/pharmacos/docs/doc2006/07_2006/def_imp_2006_07_27_en.pdf
REVISION 1 , MARCH 2011

Investigational Medicinal Product

- "a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form"

European commission: Article 2 (d) of Directive 2001/20/EC

Non- Investigational Medicinal Product

1. Within the definition of a medicinal product
2. Within the definition of a clinical trial (objective – clinical trial)
3. Intended use of the product NOT as test/ active comparator/ placebo

Non- Investigational Medicinal Product

- Products which are not the object of investigation (i.e. other than the tested product, placebo or active comparator) may be supplied to subjects participating in a trial and used in accordance with the protocol.

http://ec.europa.eu/health/files/pharmacos/docs/doc2006/07_2006/def_imp_2006_07_27_en.pdf
REVISION 1. MARCH 2011

Examples of NIMP

1. Rescue medications (ineffective, ADR, emergency)
2. Challenge medications
3. Background medications
4. Concomitant medications
5. Required to assess end points

Same level of quality and safety should be ensured for NIMPs as for the IMPs used in the trials - Same requirements as for the IMPs

http://ec.europa.eu/health/files/pharmacos/docs/doc2006/07_2006/def_imp_2006_07_27_en.pdf
REVISION 1. MARCH 2011

Background vs. Concomitant medications

- **Background medications**: Administered to each of the clinical trial subjects, regardless of randomisation group, to treat the indication which is the object of the study
- **Concomitant medications**: Given to clinical trial participants in both arms as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested, and is therefore not the object of the study.

http://ec.europa.eu/health/files/pharmacos/docs/doc2006/07_2006/def_imp_2006_07_27_en.pdf REVISION 1. MARCH 2011

A proposal ……to ERC

“ ……Section on intervention : One arm of the patients will receive “XZYREGK”

Section on control: The other arm of the patients will receive a “placebo”……”

And at the end of the trial both group of patients will be assessed for the …….

IMP

1. XZYREGK
2. Placebo

Are you satisfied with the information?

- To discuss

Working Principles

1. Research and routine care to patients cannot be measured with the same yardstick
2. A clinical trial cannot be justified ethically unless it is capable of producing scientifically reliable results
3. Sponsor and PI are responsible for IMP
4. ERCs are not “obliged” to grant approval –PI and sponsor are responsible for:
    1. Complete documentation, and
    2. Submission of adequate information

If it was not documented it means it was not done
If it is not documented it means it will not be done, But not vice versa

Working Principles

5. In multi-national clinical trials, local PI is responsible to submit “site-specific” information

6. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society *(CPMP/ICH/135/95)*

7. Some times “common sense” is better than “guidelines”!!

Requirements for an IMP depends on:

1. Intended use of IMPs
    1. Test
    2. Placebo
    3. Active comparator
2. Type of IMPs
3. Authorization status of the IMP in Sri Lanka – Applicable only to “western medicines”

Type of IMPs

- For subsequent discussion purpose
  - "Western Medicines" – which are regulated by NMRA in Sri Lanka
  - Complementary Alternative Medicines (CAM) – which are not regulated by NMRA in Sri Lanka. Examples include herbal, aurveda products, etc

Investigational Medicinal Product

- "a pharmaceutical form of an active substance or placebo being used as a reference in a clinical trial, including products already with a marketing authorization but
  - Used or assembled (formulated or packaged) in a way different from the authorized form, or
  - When used for an unauthorized indication, or
  - When used to gain further information about the authorized form"

European commission: Article 2 (d) of Directive 2001/20/EC

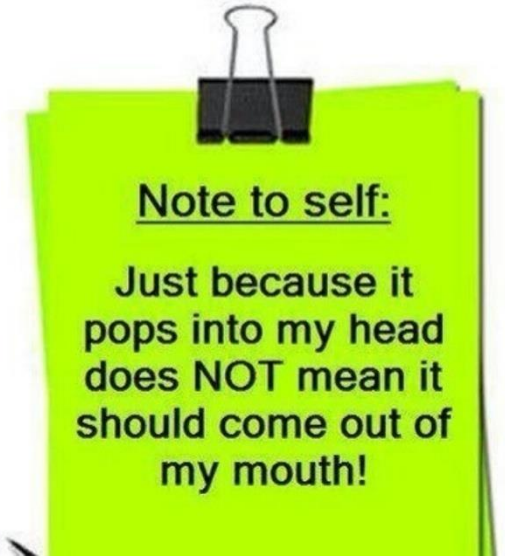
For ‘Western Medicines”, based on the authorization status of IMP in Sri Lanka

1. Product with no marketing authorization in Sri Lanka – Phase III
2. Product with a marketing authorization in Sri Lanka:
    1. Trial is for the authorized indication – to gain new information
    2. Trial is for an “unauthorized indication”
    3. Used or assembled (formulated or packaged) in a way different from the authorized form

What is this XZYREGK?

- Suppose it is a “western medicine” with a “marketing authorization” in Sri Lanka, is being tested for the “authorized” indication to get “new information”

- Justification ?
- What is this new information ?



Western Medicine, Marketing Authorization +, Tested for approved indication, to get new information

1. Brand name
2. Generic name
3. Dose
4. Dosage form
5. Route of administration (IV- Rate of administration)
6. Dosing interval / frequency
7. Duration
8. Registration status (evidence) - ? Valid

Western Medicine, Marketing Authorization +, Tested for approved indication, to get new information

9. Precautions, risks, etc
10. Exclusion criteria
11. Single source of supply
12. Who bear the cost?
13. Storage
14. Quality
15. Continuation of the supply
16. Anything more ????

Western Medicine, Marketing Authorization +, Tested for “unauthorized indication”

- 1-16 in the previous slides
- Additional information:
  - Evidence for dosing schedule
  - Justification for the new indication
  - Regulatory approval for the trial

Western Medicine, Marketing Authorization +, but formulated or packaged in a way different from the authorized form

- 1-16 in the previous slides
- Additional information:
  - Evidence for the modified formulation
  - Justification for the modified formulation
  - Regulatory approval for the trial
  - additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) to assess whether these changes would significantly alter the pharmacokinetic profile of the…….

Western Medicine, No Marketing Authorization, GCPs for IMPs

- Industry sponsored
- Results will be submitted to regulatory authorities to obtain marketing authorization
- Covers test substance, active comparator, placebo

Western Medicine, No Marketing Authorization – GCP for IMPs

1. Sufficient safety and efficacy data *(discuss)*
2. Applicable GMP
3. Coded and labelled to protect blinding
4. Labeling = Regulatory requirements
5. Storage
   - Temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion

Western Medicine, No Marketing Authorization – GCP for IMPs

6. Packing
   - To prevent contamination and unacceptable deterioration during transport and storage
7. Coding in blinded trials *(discuss)*
   - Rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding

Western Medicine, No Marketing Authorization – GCP for IMPs

8. Responsibility for the IMPs accountability at the trial site lies with the PI
9. With approval from ERC, PI can assign the responsibility for the IMPs accountability to a trial pharmacist
10. This person should main the records on IMPs
11. PI – Should ensure that the IMPs will be used as per the approved proposal
12. Should inform the correct use to the trial subject

Some examples: ? Anything worrying

- *“……..10 mg of Tablet B will be crushed and dissolved and administered to the child using a teaspoon……”*
- *“……parenteral formulation of drug C will be administered per rectally using a NG tube…..”*
- *“…….10 mg modified release formulation of drug D (Drug D- already registered and in the market) will be given three times a day……”*

Western Medicine, No Marketing Authorization – GCP for IMPs

- If significant formulation changes are made in the IMPs (test / active comparator) ……

  …… the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the……..

Supply of IMPs: Responsibilities of the Sponsor (GCP)

1. Sponsor should supply all IMPs for the trial
2. Should not supply before documentation and authorization are complete
3. Written instruction to PI about the procedures for adequate and safe:
   - Receipt, Handling, Storage, Dispensing
   - Retrieval of unused product from subjects
   - Return of unused IMPs to sponsor or alternative disposition (approved by the regulatory authority)

Supply of IMPs: Responsibilities of the Sponsor (GCP)

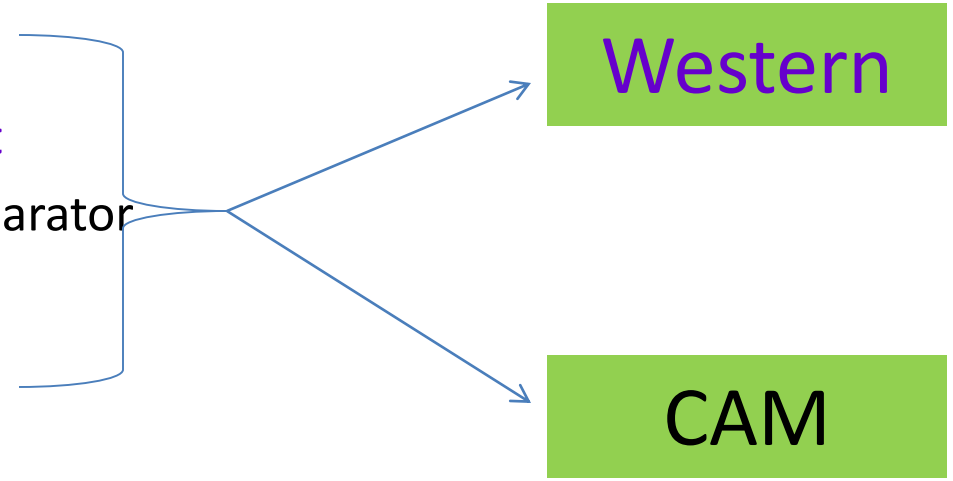
3. Ensure timely delivery
4. Maintain records
   - shipment, receipt, disposition, return, and destruction of the investigational product
5. Maintain a system for retrieval
   - for deficient product recall, reclaim after trial completion, expired product reclaim
6. Maintain a system for the disposition of unused IMPs

Supply of IMPs: Responsibilities of the Sponsor (GCP)

7. Ensuring continuous supply
8. Ensuring the product remain stable
9. Maintain sufficient quantities to reconfirm specifications (if become required)

Recall the classification

- Intervention
  - Medicinal
    - IMPs
      - Test product
      - Active comparator
      - Placebo
    - NIMPs



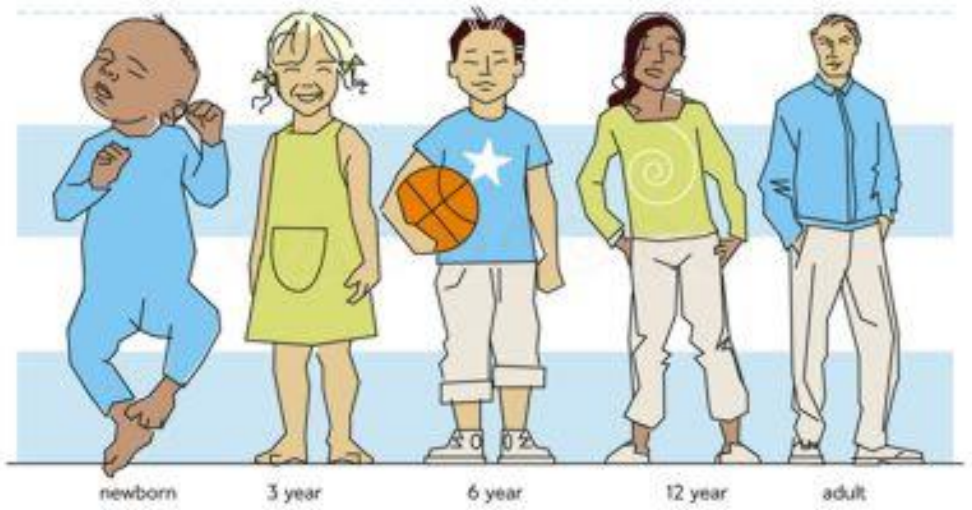
  - Non medicinal

Scope of this presentation

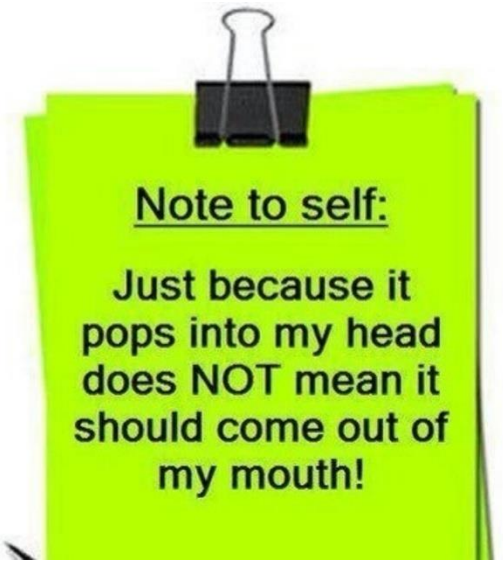
- Covered
  - Western Medicine as a test IMPs
- Not-covered
  - Western medicines as placebo and active comparator IMPs
  - Western medicines as NIMPs
  - CAMs (as IMPs or NIMPs)
  - Non-medicinal interventional products
  - Paediatric clinical trials

Paediatric Clinical Trials

- Children are not “small adults” !!!
- Children continued to be “therapeutic orphans”!!!
- Need a separate lecture – Over to you organizers



Common issues – IMPs in ERCs



1. Incomplete documentation
2. Careless compilation
3. Inadequate information to assess
4. Lack of trained personnel
5. PIs not reading the documents
6. Investigators not trained, lack of “seriousness”
7. Industry – Double standards
8. Clinical trials are equalized to routine patient care
9. Small number of experts playing different roles (ERC members, PIs, reviewers, trainers, etc) – Conflict of interests, confidentiality, transparency, etc

Placebo in clinical trials

- What are your thoughts?

Placebo in clinical trials

1. Same standards as for test product
2. ‘Sugar-pill” (? For diabetics)
3. Looks, and tastes like the test product
4. Office for human research protection (OHRP)
5. Must be justified by positive risk – benefits analysis
6. Subjects/ participants should be fully informed of the risks involved in the assignment into the placebo group
7. Continued assignment of subjects to placebo is unethical once there is good evidence to support the efficacy of the test substance

Placebo in clinical trials

8. Increased monitoring to detect deterioration and the use of rescue medication to be stated in the proposal
9. Early escape mechanisms and explicit withdrawal criteria should be incorporated into the trial design
10. Number of subjects in placebo arm must be kept smaller than the number in the active treatment arm
11. “Add on” method
12. If prolonged period on placebo is unacceptable, use it initially for shorter period, after that without placebo

Placebo in clinical trials

13. DMSB
14. Information sheet:
    - All aspects about placebo should be included
    - Under risk: Condition may worsen while on placebo should be included
    - Under benefit: Subjects in the placebo group will not receive the same benefit as those who receive active treatment if that treatment is effective should be included