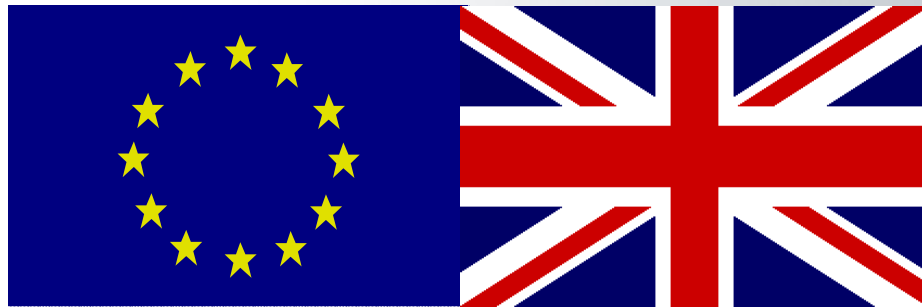


Research Governance: In Practice

By Gill Sims



Practical Implications



- Protocol Development / Study Set up**

- CTIMP Specific

- Safety Reporting

- Consent

- Management and Monitoring

- Data Security and Archiving

Protocol Development / Study Set up



- Protocol must be written to the standards of ICH GCP
For ICH Compliant Protocol go to:

[Protocol template 1](#)

[Protocol template 2](#)

- Discuss with Research Governance / R & D Manager at an early stage:
 - Agree a Research Sponsor*
 - Risk Assessment:
 - Consider the need for:
 - Independent Data Monitoring Committee
 - Trial Steering Committee
 - Agree safety reporting systems

Practical Implications



Protocol Development / Study Set up

CTIMP Specific

Safety Reporting

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Data Security and Archiving

CTIMP specific



MHRA authorisation

- A Clinical Trial Authorisation must be in place before the start of the study
- Cost involved (see hand out for details)
- 60 day time frame
 - Obtain a protocol number before applying (from sponsor)
 - Obtain EUdraCT Number [Get a EUdraCT Number](#)
 - Apply using IRAS [Apply for a CTA via IRAS](#)
 - Need Help? e-mail [Get Help from MHRA](#)

GMP Compliance

- A specific requirement of the Clinical Trials Directive
- All hospital pharmacy processes and procedures must comply
- Annex 13 provides full details
- MHRA inspectors require confirmation of GMP compliance in addition to GCP

Labelling of IMP's

Protocol No. or Study No
Subject No
Investigator:

Route of administration
Quantity/ Dosage
Product description
Lot No.

Use By:
Storage conditions
Keep out of Reach of Children
For Clinical Trial Use Only

Sponsor Address

Scope of the Directive



The Directive defines a Clinical Trial as:

“... any investigation in human subjects, other than a non interventional trial intended

- To discover or verify the clinical, pharmacological, or other pharmacodynamic effects of one or more medicinal products
- Identify adverse reactions
- Study absorption, distribution, metabolism and excretion

With the object of ascertaining the safety or efficacy of the product, or those products

What is an 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 authorisation but used or assembled (formulated or packaged) in a way different from the authorised form,

or when used for an unauthorised indication,

or when used to gain further information about the authorised form”

Non - Interventional Trial



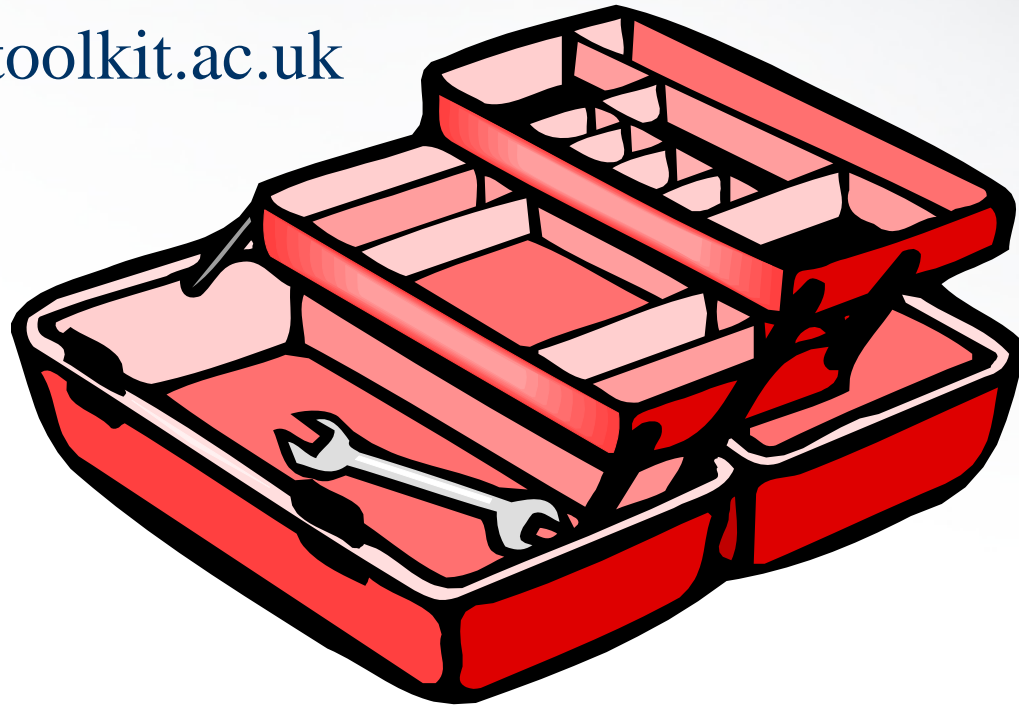
The Directive does not apply to apply to non interventional Trials, i.e.

- A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation.
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study.
- No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis

Getting help !!



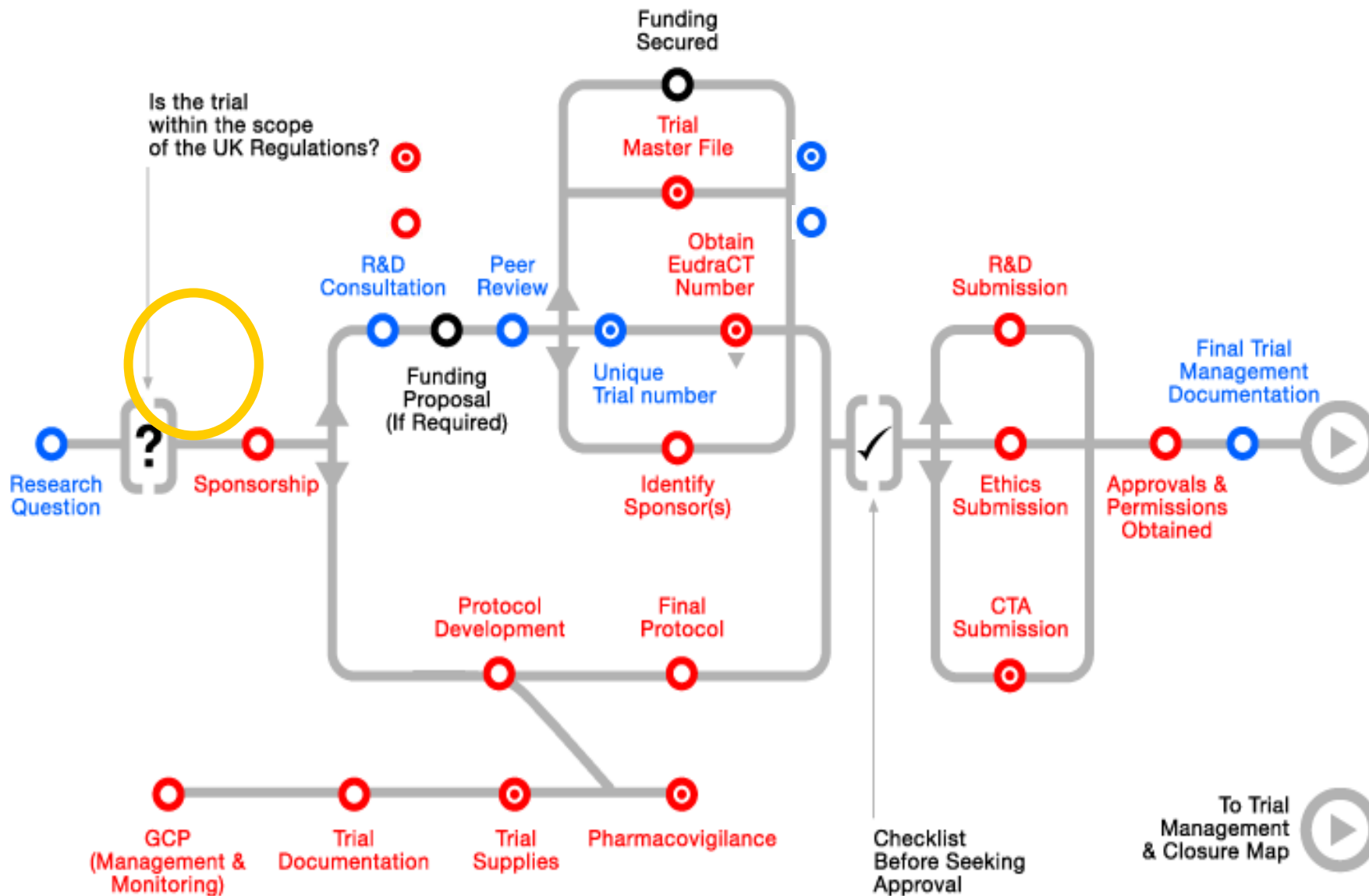
Clinical Trial Tool Kit
<http://www.ct-toolkit.ac.uk>



[Clinical Trial Tool Kit](#)

[Question & Answers](#)

MRC/ DH Clinical Trial Tool Kit



Practical Implications



Sponsorship

CTIMP Specific

Safety Reporting

Consent

Management and Monitoring

Data Security and Archiving

Safety Reporting

Who is responsible?



Reporting to Sponsor

- ❑ The Investigator is responsible for reporting all Serious Adverse Events immediately to the sponsor (CTIMP and Non CTIMP studies)

However:-

- ❑ CTIMP : Serious Adverse Events listed in the Protocol as not requiring immediate reporting are exempt from this requirement

Safety Reporting:

Who is responsible?



Reporting to MHRA

- ❑ The **Sponsor** is responsible for reporting SUSAR's within the specified time frames
- ❑ NB As a general rule, in blinded studies, treatment codes should be broken by the sponsor before reporting to the MHRA and Ethics

Reporting to other Investigators

- ❑ In a multi site study the **Chief Investigator** is responsible for ensuring all PI's are made aware of SUSAR's occurring at other sites.

Reporting to Ethics

- ❑ **CTIMP**
All SUSAR's must be reported to ethics:
Same time frames as MHRA
- Non-CTIMP:** 15 days
Either the **Investigator / or Sponsor** can report

How to report SUSAR's to MHRA

❑ Use CIOMS 1 form

❑ Initial report must include:

- A suspected IMP
- An Identifiable subject (e.g. trial no)
- An Adverse Event assessed as Serious and unexpected, for which there is a reasonable suspected causal relationship
- An identifiable reporting source

[CIOMS 1 Form](#)

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (Last, First) 1a. COUNTRY 2. DATE OF BIRTH (Day, Month, Year) 3. AGE (Years) 4. SEX (Day, Month, Year) 5. REACTION ONSET (Day, Month, Year) 6. CHECK ALL APPROPRIATE TO ADVERSE REACTION

7. DISCIBEL REACTION(S) including relevant test(s) (date)

PATIENT DIED
 INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
 INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
 LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) 20. DID REACTION ABATE AFTER STOPPING DRUG? (YES, NO, L, NA)

15. DAILY DOSE(S) 18. ROUTE(S) OF ADMINISTRATION 21. DID REACTION REAPPEAR AFTER REINRODUCTION? (YES, NO, NA)

17. INDICATION(S) FOR USE 19. THERAPY DURATION

18. THERAPY DATES (Start to End) 19. THERAPY INTENTION

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (include those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER 24d. REPORT SOURCE (STUDY, HEALTH PROFESSIONAL)

DATE OF THIS REPORT 25a. REPORT TYPE (Initial, Follow-up)

Reporting SUSAR's



Postal reports must be sent to:

UK Clinical Trials SUSAR

Reporting

MHRA

PO Box 20

Mitcheldean

GL17 OWQ

Alternatively reports can be scanned as pdf and e-mailed to

pharmacovigilance@mhra.gsi.gov.uk

You must clearly state that the attachment is a UK Clinical Trial SUSAR.

Existing fax facility:

0207084 2443

Annual Safety & Progress Reports



- Ethics require annual Safety and Progress reports for all research
- MHRA Require Annual Safety Reports
- Reports must be submitted by or on behalf of the sponsor and must be signed by the CI

Ethics progress and Safety Reports

MHRA Safety Reporting

- Notify Ethics of end of trial: within 90 days
- If Trial stopped early: within 15 days

Practical Implications



Sponsorship

CTIMP Specific

Safety Reporting

Consent

Management and Monitoring

Data Security and Archive

Consent



Valid if

- Voluntarily and freely given
- Fully informed
- Participant has capacity



AWARENES OF RANDOMISATION CAN COUNTER RESULTS

(Declaration of Helsinki 2002)

(ICH GCP (1996))

Definition of Informed consent (CTIMP)



A person gives informed consent to take part in a clinical trial only if his decision:

- (a) Is given freely after that person is informed of the nature, significance, implications and risks of the trial; and
- (b) either:
 - (i) Is evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his consent, or
 - (ii) if the person is unable to sign or to mark a document so as to indicate his consent, is given orally in the presence of at least one witness and recorded in writing.

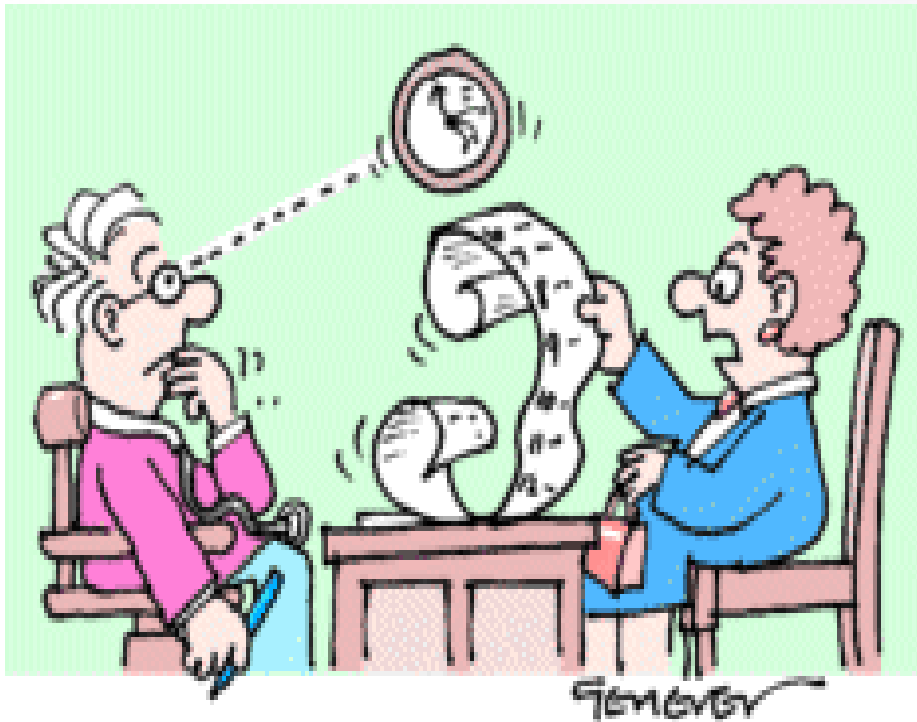
SI1031. 3(1) Schedule 1

NB: The same definition applies to the giving of informed consent by a legal representative

Informed Consent



Essential elements of a PIS



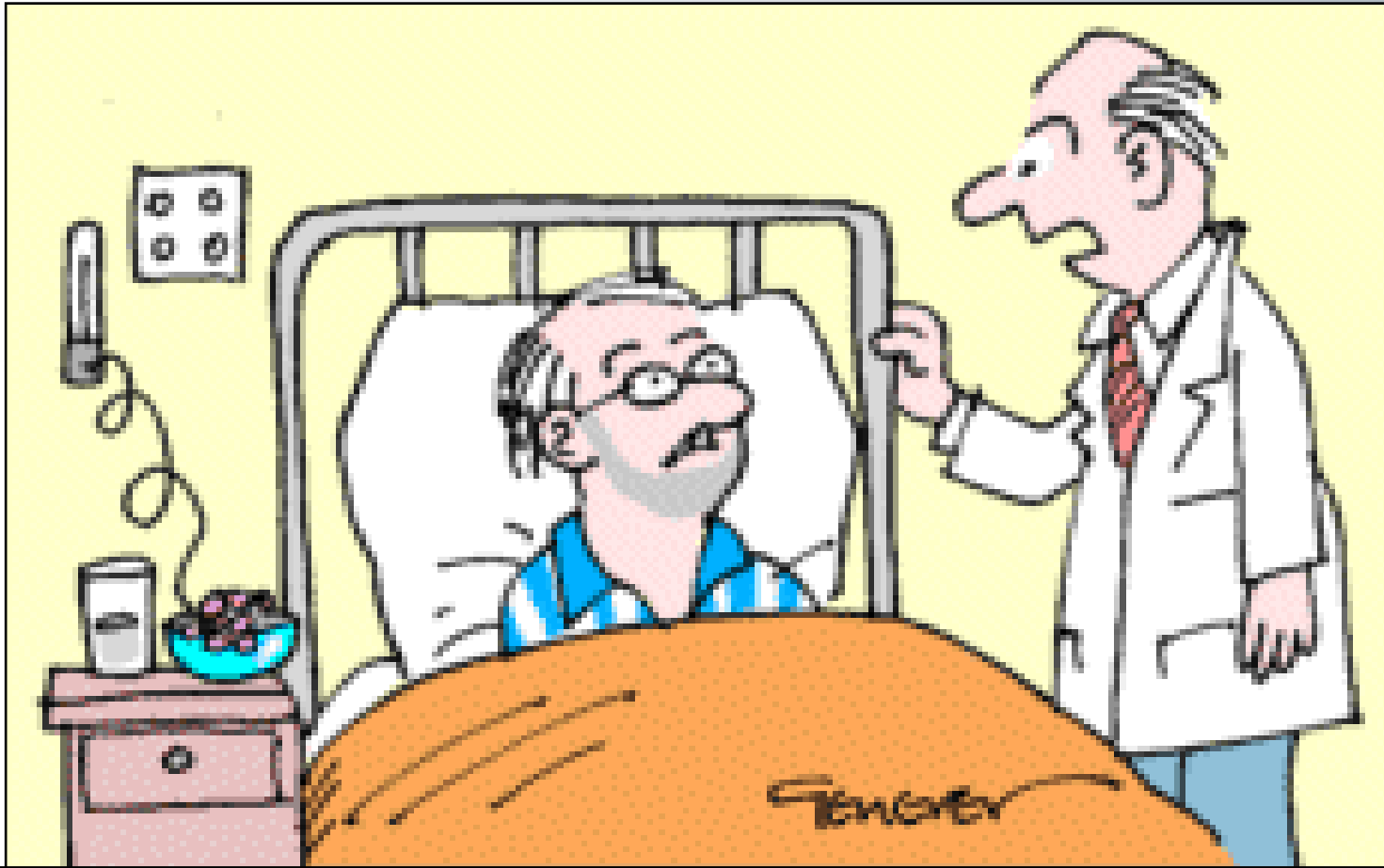
- ❑ Consideration of consenting practices is a high priority of ethics committee review
- ❑ **Contents of PIS**
Must comply with Data Protection law:
Legally required to provide data about how the participant's personal data will be used and who will have access to the data
- ❑ Must include:
 - Purpose of the study
 - Benefits and risks, Likely discomfort (When there is no intended clinical benefit to the participant, the participant must be made aware of this)
 - The right to withdraw consent without reprisal
 - CTIMP – *“Must be provided with a contact point where he may obtain further information about the trial”*

And much more !

For full details go to:

[PIS Guidance](#)

Who can obtain informed consent?



' Thanks for telling me your entire medical history but I'm the hospital barber. '

Who should seek consent?



15

“Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person...”

22

*“After ensuring that the subject has understood the information, the **physician** should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.”*

Declaration of Helsinki

Who should seek consent?



4.8.8

“Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion”

2.7

“The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.”

Consent for adults who lack capacity



Non - CTIMP

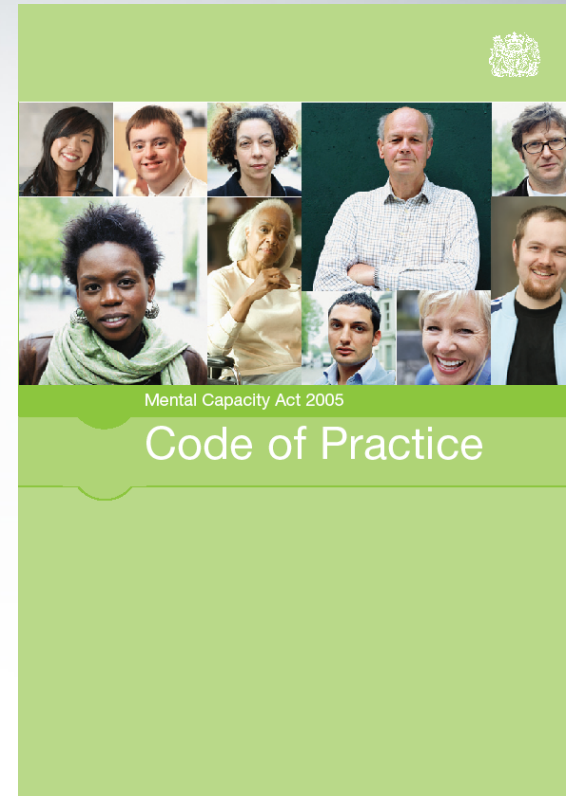
Governed by the Mental Capacity Act (2005)

Required to comply with the Code of Practice:-

- ❑ **must** be related to the condition that contributes to the impairment of the mind or brain from which the incapacitated person is suffering
- ❑ **must** be approved by a Research Ethics Committee (REC)
- ❑ **must** not be possible to conduct the research involving individuals who retain the capacity to consent.

Before an incapacitated individual can be enrolled in research, the researchers must identify somebody close to them who is willing to be consulted about the appropriateness of his or her involvement.

[Guidance Consent for those who lack capacity](#)



Consent for adults who lack capacity



CTIMP

Must comply with the Clinical Trial Regulations:

- written consent required from a legal representative before participation in the Trial clinical trial
- There are grounds for expecting that administering the medicinal product to be tested in the trial will produce a benefit to the subject outweighing the risks or produce no risk at all.
- The clinical trial relates directly to a life-threatening or debilitating clinical condition from which the subject suffers.

Or

- The clinical trial is essential to validate data obtained - in other clinical trials (or other type of research) involving persons able to give informed consent,

Exception In emergency situations



Exempt from the need to obtain consent from a legal representative before the trial commences

The exception applies only when the following conditions are met:

- treatment is required urgently;
- the nature of the trial also requires urgent action;
- It is not reasonably practical to obtain consent prior to the start of the study
- An appropriate Ethics committee has approved the study

The Medicines for Human Use (Clinical Trials)
Amendment (No.2) Regulations 2006

Practical Implications



- Sponsorship
- CTIMP Specific
- Safety Reporting
- Consent
- Management and Monitoring**
- Data Security and Archive

Study Management



- PI responsible for day to day management at a research site
- Study must be conducted according to approved, current version of the protocol
- CI Must ensure all approvals are in place before starting a study
- CI Responsible for ensuring clinical trials ^{*} are registered on a publicly accessible database – before recruitment of first subject
WHO : October 2008
- ICMJE – require above as a prerequisite of any subsequent publication.
[Medical Journal Editors](#)
- Substantial amendments
 - must be approved by the Ethics committee (all versions must be dated and have a separate version number)
 - Ethics must reply within 35 days
 - Amendments relating to urgent safety measures can be implemented immediately[Ethics substantial amendment form](#)
- Sponsor must be informed of and agree all amendments
- PI/CI and Sponsor are jointly responsible for maintaining the ‘Essential Documents’ for the study ...

Study Management



Essential Documents

“Those documents that individually or collectively permit evaluation of a trial and the quality of the data produced”

ICH GCP E6 / E8

- Essential documents must be kept in a study Site File
- Site File must be established at the beginning of a study, both at the investigator institution and the sponsor’s office

ICH GCP E6

Master Site File



Investigator File must contain:

Before start of study:

- Signed Protocol and amendments
- Sample CRF
- Information given to patient
- Insurance statements
- CV's of Investigators and support staff
- Signature sheets of all those authorised to make amendments
- Normal Value Range for Med/lab/tech procedures
- Sample of labels (CTIMP only)

During the study:

- Subject Screening log
- Subject enrolment log
- Signature sheet of all those authorised to make entries

*MHRA
Inspection

*

At study end

- Retention time frames
- Archive information

Monitoring



What is it?

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCPs, and the applicable regulatory requirements)

(ICH GCP1.38)

Monitoring: Purpose



To verify that...

- The rights and well-being of human subjects are protected
- The reported trial data are accurate, complete and verifiable from source documents
- The conduct of the trial is in compliance with protocol, GCP, and applicable regulator requirements

Monitoring



- ❑ Sponsor shall monitor progress of its studies (ICH 5.18.3)
- ❑ Research Governance Framework requires 10% of research studies to be monitored (minimum)
- ❑ Systems for monitoring should be developed during protocol development (agreed between the study team and sponsor)
 - ❑ 100% Source Data Verification not always required
 - ❑ Amount and type of monitoring should be based on a study risk assessment
 - ❑ Vulnerability of population
 - ❑ Volume of patients
 - ❑ Type of medicinal product / Device
 - ❑ Phase of study
- ❑ Consider how monitoring is to be funded

MHRA Inspectorate



- Assess compliance with legislation and guidelines relating to the conduct of clinical trials involving IMP's:
- Carrying out inspections of sponsor organisations and sites that provide services to clinical trial sponsors
- Three types:
 - Triggered
 - Routine
 - Pre marketing application
- Rights:
 - To enter any premises involved in CTIMP
 - To carry out inspection of such premises
 - To take samples, require the production of books and documents – seize & detain substances, articles & documents
 - It is a criminal offence to obstruct an inspector during the conduct of an inspection
- Not Free !!
- If Critical Findings ++ They may re inspect (further fees)
- Hold a warrant - Maximum penalty for non compliance – 2 year prison sentence!



Practical Implications



Sponsorship

CTIMP Specific

Safety Reporting

Consent

Management and Monitoring

Data Protection and Archive

Data Protection



Applicable law

- ❑ Data Protection Act 1998
- ❑ Caldicott Report (1997)
- ❑ Human Rights Act (1998)
- ❑ Health and Social Care Act (2001)
 - Section 60 Support
 - Patient Information Advisory Group
- ❑ Patient samples form part of the patient record and thus must comply with data protection regulations and the Human Tissue Act (2004)

Data Protection



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 - **Section 60 Support**

 - **Patient Information Advisory Group**

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DP Principles (8)



1st Principle (fair and lawful processing)

- ❑ Obligation to provide information

Minimum information:

- ❑ Identity of the Data Controller (organisations who will be processing the data)
- ❑ Purposes) for which the Personal Data (PD) will be used
- ❑ If PD is to be sent outside the EEC the data subject must be informed.

DP Principles(8)



2nd principle (specified purposes)

- ❑ PD shall be processed for one or more specified purposes and shall not be further processed in any manner incompatible with that purpose (purposes)

Research exemption to conditions of further processing provided that:

- ❑ Data not processed to support decisions about a particular individual

AND

- ❑ Not processed in such a way that substantial damage or distress is likely to be caused to any individual.

DP Summary



Data Security

- Personal Data must be anonymised wherever possible
 - Access must be restricted
 - Secure, password protected computers
 - Paper files stored in locked filing cabinet
- (7)

Data Storage

Personal data must only be stored for as long as is necessary

(5)

Data Collection

Data must be adequate, relevant and not excessive
(consider this when designing CRF's)

(3)

Consent and Patient Information Requirements

Research Participants must be provided with adequate information about how their data is to be used and who will have access to data that identifies them

(1)

The use of Personal Data without consent e.g. secondary use of existing data requires approval under s251 of the NHS Act 2006 (formerly “section 60 support” under the Health & Social Care Act 2005)) [NIGB Ethics and confidentiality](#) [Patient Information Advisory Committee](#)

(8)

Safe Transfer of Data

The Act requires that personal data is not transferred outside the EEC unless the country it is being transferred to has equivalent levels of protection. careful consideration required when transferring data outside the EEA. This information must be provided on the patient information sheet.

Human Tissue Act (2004)



- ❑ Governs the use of Tissue for Scheduled purposes (Research is a scheduled purpose)
- ❑ Consent is the fundamental principle underpinning the lawful processing of body parts, organs or tissue for health related purposes (for the living and deceased)
- ❑ Exemptions to consent requirements:
 - ❑ Removal of tissue from the living is covered under common law (no different to before the 2004 Act)
 - ❑ Retention and use of tissue which was retained prior to September 2006 (Consent not required)
 - ❑ Retention and use of anonymised tissue – consent not required providing the study has ethics approval (this includes the use of residual tissue taken from the living)
- ❑ Licence requirements for storage
 - ❑ Not required if storing organs, tissue or cells in connection with a specific, ethically approved study
 - ❑ Not required if the material you are storing was created outside the human body (e.g. cell line)

NB: PIAG /NIGB approval might be required if tissue is being used in association with patient data (where no consent has been given for the use of the data).

Link :- [Data and Tissue Tool Kit](#)

Archiving Data



CTIMP undertaken with a view to marketing

Sponsor Specific Essential documents (including CRF's) must be retained for or at least 2 years after the last approval of a marketing application in the EU

Commission Directive 2003/63/EC

CTIMP not intended for marketing & Non CTIMP

retained for at least five years after completion of the study. These documents should be retained for a longer period if required by the Sponsor, the funder or other regulatory authority

- NB: MRC requirement is a minimum of 20 years for clinical or public health studies. It is important to check with the funder / sponsor to be sure you meet their requirements

- Essential Documents should be readily available, upon request, by the CA.
- Sponsor must appoint someone to have responsibility for archiving
- Transfer of ownership to be documented
- Record of destruction must be kept for a five years.

Question 1



“Any untoward medical occurrence in a patient or clinical trial subject administered a medical product and which does not necessarily have a causal relationship with this treatment” Is a definition of which of the following:

- o *Adverse Event*
- o *Adverse Reaction*
- o *Serious Adverse Event*
- o *Unexpected Adverse Reaction*

Question 2



Which of the following is INCORRECT?

- *The Directive applies to bioequivalence studies*
- *The Directive applies to academic trials*
- *The Directive applies to non-interventional studies*
- *The Directive applies to bioavailability studies*

Question 3



How long does the sponsor have to notify the competent authority that a clinical trial, that has not been terminated early, has ended?

Within 90 days

Within 60 days

Within 30 days

Within 15 days

Question 4



Which of the following reporting requirements is INCORRECT?

- o All Suspected Unexpected Serious Adverse Reactions that are life threatening must be reported to the Competent Authority and the Ethics committee no later than 7 days after first knowledge by the sponsor*
- o Follow up information on all Suspected Unexpected Serious Adverse Reactions that are fatal or life threatening must be received by the MHRA within an additional 8 days*
- o At the end of a trial the Sponsor has to provide a list of suspected Serious Adverse Reactions to the Ethics Committee*
- o Suspected Unexpected Serious Adverse Reactions that are not fatal or life threatening will be reported to the Competent Authority and the Ethics committee within 15 days of the sponsor first becoming aware of them*

Question 5



How long does an Ethics Committee have to reply to a request for a substantial amendment?

o 30 days

o 60 days

o 35 days

o 65 days

Please don't despair...
There is light at the end of the tunnel
(Honest) !!



Thank you

Any Questions?

