

GCP for Emergency Medicine

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- **This presentation is intended for emergency physicians involved in recruiting patients to clinical trials and/or caring for patients who are in clinical trials**
 - **It covers the essential elements of research governance, the EU Directive on Clinical Trials and ICH-GCP**
 - **Emergency physicians who are involved in clinical trial management will need additional training and should contact their local research office**
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 - Informed Consent
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Core knowledge for emergency medicine

- **Pragmatic research is essential to develop the evidence base for emergency medicine**
- **Pragmatic research requires integration of research and routine clinical practice**
- **Knowledge of ICH-GCP is necessary for physicians with any involvement in research**
- **This presentation provides core knowledge about ICH-GCP for emergency physicians**

ICH-GCP

- ICH is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
 - ICH-GCP is Good Clinical Practice guidelines agreed at the conference
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ICH definition - GCP

"A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected"

ICH E6 1.24

The Objectives of ICH GCP Guidelines

- **Developed with consideration of the current good clinical practices of the European Union, Japan & USA, plus those of Australia, Canada, the Nordic countries & World Health Organisation.**
- **Provide a unified standard for the European Union, Japan & USA to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.**

Good Clinical Practice - GCP

- **What is GCP?**

- Ethical and scientific quality standards for designing, conducting, recording and reporting trials that involve participation of human subjects

- **Why is it needed?**

- To ensure that the RIGHTS, SAFETY and WELLBEING of the trial subjects are protected
- Ensure the CREDIBILITY of clinical trial data

- **Why has it developed into formal guidelines?**

- Public disasters, serious fraud and abuse of human rights

ICH GCP Guidelines cover...



Ethics Committee

Investigator

Sponsor

**Clinical Trial
Protocol &
Amendments**

**Investigator's
Brochure**

**Essential
Documents
for conduct
of a trial**

Declaration of Helsinki

- **World Medical Association June 1964 (Helsinki, Finland)**
 - **Forms the basis of ICH-GCP**
 - **Covers all “medical research” - makes specific provision for emergency care research**
 - **Most recent amendment October 2000**
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Relevance to the emergency physician

- **ICH-GCP covers the following:**
 - Ethics & informed consent
 - Investigational products
 - Medical care of trial subjects
 - Randomisation
 - Maintaining records
 - Adverse event reporting
 - Unblinding
- **All put together in the research Governance Framework**

Research Governance Framework

Scope of the Framework

- **The Framework covers:**

- Research by staff with Trust and Honorary Trust Contracts
- Research involving patients, service users, care professionals, volunteers or their organs, tissues or data
- Research funded by the NHS
- Research using facilities funded by the NHS

Aims of the Framework

- **To promote a quality research culture**
- **To promote excellence**
- **To provide strong leadership for research**
- **To implement standards:**
 - set out in legislation and regulations
 - required by the Department of Health
 - established as good practice

Research Governance domains

- **Ethics**
- **Science**
- **Information**
- **Health, Safety and Employment**
- **Finance and Intellectual Property**

Ethics - key points

- **Research involving patients, service users, care professionals, volunteers, or their organs, tissues or data should be independently reviewed by an ethics committee**
 - **Consideration should be given to the dignity, rights, safety and well being of participants**
 - **Participants should give informed consent**
 - **Participant data should be protected**
 - **Consumers should be involved in research**
 - **Diversity of human culture should be respected**
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Science - key points

- **Proposed research should be independently peer reviewed – commensurate with the scale of research**
 - **Research should be regulated, where appropriate, by the relevant agency (e.g. MHRA for drugs)**
 - **Data should be retained to allow further analysis and support monitoring**
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Information - key points

- **There should be free access to information on research being conducted and research findings**
 - **Results should be published in a format understandable to the public**
 - **Findings should be made available to participants**
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Responsibilities

- **Within the Framework are defined responsibilities for:**
 - The Researcher
 - The Sponsor
 - The Care Organisation

The Researcher is responsible for:

- **Developing proposals**
- **Seeking ethical committee approval**
- **Conducting research according to the agreed protocol**
- **Ensuring participant welfare**
- **Feeding back results to the participants**

The Sponsor is responsible for:

- **Assuring scientific quality (peer review)**
- **Ensuring research ethics committee approval**
- **Ensuring arrangements for the management and monitoring of research**

The Care Organisation is responsible for:

- **Ensuring that research using their patients, users, carers or staff meets the standards in the Research Governance Framework**
- **Ensuring ethics committee approval**
- **Retaining responsibility for research participants' care**

Sanctions

If the Researcher, Sponsor or Care Organisation do not fully meet their responsibilities the research will be stopped.

**The EU Clinical Trials Directive
2001/20/EC and the Mental Capacity
Act 2005**

The EU Clinical Trials Directive

- Incorporated into UK law through the Medicines for Human Use (Clinical Trials) Regulations 2004
- Aims to harmonise clinical trial legislation throughout the EU
- Covers all trials of medicinal products
- ICH-GCP is to be the GCP standard (EU GCP Directive 2005)
- Requires all trials of medicinal products to be regulated by a competent authority – in the UK this is the Medicines and Healthcare products Regulation Authority (MHRA)

EU Directive & Informed Consent

- **Standards currently adopted in the UK comply with the Directive**
- **However, the Directive states that a “legal representative” may act for a trial subject that is not able to give informed consent**
 - **A formal mechanism to appoint a legal representative for incapacitated adults has been introduced**
- **This is relevant to incapacitated adults in emergency medicine**

Mental Capacity Act 2005

- The **Mental Capacity Act 2005** provides a statutory framework for people who lack capacity to make decision for themselves
- The code has statutory force and certain categories of people have a legal duty to have regard to it, including those carrying out research approved in accordance with the act
- Before starting research, the research team must make arrangements to
 - ❖ Obtain approval from an appropriate body (REC)
 - ❖ Consult with carers or other relevant people
 - ❖ Exception to the duty to consult can be granted for research into procedures or treatments used in emergencies

- **The MHRA have produced a short description of 'The Medicines for Human Use (Clinical Trials) Regulations 2004' (the UK order which implements the EU Directive) which aims to help those involved in the conduct of clinical trials to follow and understand the Regulations**
- <http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2022633.pdf>

- **In essence the Medicines Regulations and the Mental Capacity Act have exactly the same structure - but the terminology is different**
- **Both provide for an independent person to give consent if the patient cannot**
- **Both provide for trial entry without consent in an emergency, as long as this has been approved by the Research Ethics Committee**

Consent

What is Informed Consent?

"Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate"

ICH 1.28

Who can consent a subject?

- A medically qualified person (usually) - however, Declaration of Helsinki states “physician”
- Nurses and allied health professionals may be granted the right to take consent for a specific trial, provided they are appropriately trained
- Consent may be delegated to a sub investigator (needs to be documented) – must have be approved by the ethics committee
- The Investigator retains overall responsibility
- Consent must be documented in the medical notes

When should a subject be consented?

- **Prior to participation in a trial**
- **Before ANY trial procedure - including the taking of blood to screen patients if it is not part of normal clinical practice or a questionnaire to access health etc**
- **Specific exceptions may be allowed in emergency situations**

How should someone be consented?

- **The consent form must have been approved by the Ethics Committee**
- **The process must have been approved by the Ethics Committee**
- **There should be no coercion to enter the trial**
- **Non-technical language must be used**
- **The information must be presented to the subject in the most appropriate way**
- **The subject must have “ample” time to consider their decision**

How should a consent form be completed?

- **Subject must sign & date the form (& preferably write their own name)**
- **Original patient information leaflet & consent form - site file**
- **Copies of patient information leaflet and & consent form - Patient notes and to the patient**
- **The consent form & patient information leaflet should always be kept together**

Consent in Emergency Trials

- **The introduction of the Mental Capacity Act 2005 introduced a formal mechanism to appoint a legal representative for incapacitated adults**
- **If prior approved by the ethics committee:**
 - ❖ **A legal representative (relative, friend or doctor) can give consent on behalf of the patient**
 - ❖ **No consent or an oral consent can be obtained initially, with full written consent obtained later**

Safety & Adverse Events

Safety Data collected in Clinical Trials

- **Adverse Events**
- **Serious Adverse Events**
- **Adverse Reactions**
- **Suspected / Unexpected Serious Adverse Reaction**
- **Pregnancy**
- **Lab data**
- **Vital Signs**
- **Project specific data**

An Adverse Event (AE) is...

- **Any untoward medical occurrence**
- **Not necessarily causal relationship with treatment**
- **Unfavourable / unintended sign**

A Serious Adverse Event (SAE) is an AE that...

- **Results in death**
- **Is life threatening**
- **Requires hospitalisation or prolongation of stay**
- **Results in persistent or significant disability/incapacity**
- **Consists of congenital anomaly or birth defect**

SAE definitions

- **Results in death**

- Record the event that lead to death as the SAE
- “Death” is the outcome

- **Life threatening**

- “The patient was, in the view of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death”

SAE definitions

- Prolonged hospitalisation
 - Record diagnosis **NOT** procedure
 - Hospitalisation means **in-patient admission**
 - Not out-patient appointments or ED visits
- Disabling or incapacitating
 - **Event which is disabling or incapacitating or causes a disruption of one's ability to carry out normal life functions or daily activities**

SAE definitions

- **Prolonged hospitalisation**

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SAE definitions

- **Congenital anomaly**

- Diagnosed in the offspring of a subject who received study drug

- **Other**

- Additional option given by some pharmaceutical companies
- Event not covered by SAE categories but in the investigator's opinion, should be considered serious

A Suspected Adverse Reaction (SAR) is...

- **Untoward or unintended response to the medicinal product under investigation**

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is...

- **A serious adverse reaction**
- **Unexpected = not consistent with information already available in the protocol and the Investigators Brochure**

Adverse event reporting

- Will depend upon the trial and be defined in the protocol
- Generally any AE or SAR should be recorded in the patient notes and Case Report Form and reported to the Principal Investigator (PI) at the study site
- The PI determines whether the AE or SAR is serious
- The PI informs the Chief Investigator (multicentre studies) of any SAE or SUSAR
- The Chief Investigator will report any SAE or SUSAR to the Trial Sponsor, Data Monitoring Committee, MHRA and/or Ethics Committee, as specified in the protocol

Documentation & Audit

Essential Documents

“Are those documents, which permit evaluation of the conduct of the trial and the quality of data produced.

These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP and with all regulatory requirements”

ICH (8 .1)

Essential Documents

- **Are audited by the regulatory authorities or sponsor company to confirm the validity of the data & integrity of the data collected**
 - **Are contained in the files established at the beginning of the trial at sponsors office and investigators site**
 - **For the minimum list - see ICH section 8**
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Essential Documents - source data

- **Records should be accurate, complete, legible & timely ICH (4.9.1)**
- **Data should be consistent with source documents (or discrepancies explained) ICH (4.9.2)**
- **Any changes should be initialled, dated & explained**
- **Document all deviations from protocol and explain ICH (4.5.3)**
- **Document all dose/therapy modifications, visits and tests not conducted**

What needs to be recorded in the patient notes?

- **Copy of signed and dated Consent Form and Patient Information Leaflet**
- **Title of the trial including the drug to be received**
- **Study and patient number**
- **Visit dates**
- **Concomitant medicines taken**
- **Any adverse events**
- **A letter informing the GP that the patient has been enrolled in the clinical trial**

Essential Documents availability

- **Essential documents should be retained for 2 yrs following last approval of marketing application in the ICH region (taken to be 15yrs)**
 - ICH (4.9.5)
- **All records must be made available (direct access) for monitors, auditors & regulatory authorities**
 - ICH (4.9.7)

ICH definition - Audit

"a systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)"

ICH E6 1.6)

Common audit findings

- **Patients do not fulfil the entry criteria**
- **Incomplete/incorrectly completed consent forms**
- **Drug accountability inadequate**
- **Hidden entry envelopes opened during study**

In summary

- **ALL clinical research in emergency medicine should take place within the Research Governance Framework**
 - **ICH-GCP is core knowledge for emergency physicians and essential for those involved in research**
 - **Emergency physicians involved in research must have a good understanding of the principles of informed consent, adverse event reporting and study documentation.**
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Further Reading

What to do now?

- 1) Read the document “Principles of ICH-GCP”
- 2) Read the article on consent in EM research:
<http://emj.bmj.com/cgi/content/full/23/12/893>
- 3) Read the Research Governance Framework:
[Research governance framework for health and social care: Second edition :
Department of Health - Publications](#)
- 4) If you have any questions or feel that you need further training please contact your local Trust R&D Office.
- 5) Print out and sign the declaration on the document “CEM GCP Certificate”