Fundamentals of Clinical Research Delivery for Administering IMPs
Welcome

• The importance of clinical research

• The importance of administering medicines in clinical research

• Practice standards

• Roles and responsibilities

• Documentation and data

• Considerations specific to administering medicines in clinical research
The importance of clinical research
Why is clinical research important?

“Research is central to the NHS...

We need the evidence from research to deliver better care. Much of the care that we deliver at the moment is based on uncertainties or experience, but not on evidence.

We can only correct that with research.”

– excerpt from NIHR video
Enhancing Patient Care Through Research

Professor Dame Sally Davies, Chief Medical Officer for England, Director General of Research and Development and Chief Scientific Adviser for the Department of Health and NHS.

CMO Wales Dr Frank Atherton
Research is a frontline service

The NHS is committed to continuous improvement in the quality of services [patients] receive, identifying and sharing best practice in quality of care and treatments.
Example: the importance of administering medicines in clinical research

The development of Herceptin, the brand name of a medicine called trastuzumab

Research Idea

Research discovered that HER2 was amplified in some cancers and was associated with poorer outcome

HER2 became a good target for drug development
Example: the importance of administering medicines in clinical research

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HER2 became a good target for drug development.

A monoclonal antibody drug was developed to block the receptor activity of HER2.

The monoclonal antibody drug eventually became known as trastuzumab (brand name Herceptin), and was tested in clinical trials.
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Clinical Trials

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Treatment

Herceptin is now commonly used to treat pts who are HER2+

HER2 testing now routine in NHS practice.
Research is important to patients

How important is it to you that the NHS carries out clinical research?

- 94% Very/fairly important
- 1.9% Not important
- 4.7% Don’t know

How important is it to you to be offered new treatments by your healthcare professional?

- 93% Very/fairly important
- 2.4% Not important
- 5% Don’t know

Results are taken from a Censuswide consumer poll of 3,000 people in England, commissioned by NIHR CRN in September 2014.
Inspirational experiences from patients, their families and carers

We've gathered some fantastic stories from people across England, whose lives have been transformed by clinical research. All you need to do is click on the links below to access experiences relating to a wide range of conditions. You'll find short-films and video diaries to explore, plus audio and written accounts too.

If you want to tell us about your experiences, please email the team at cmcc.communications@nihr.ac.uk

You can also join the conversation on Twitter: Share your experiences with @nihr.ac.uk using #rclm.

Health and Care Research Wales

VISION

Our vision is for Wales to be internationally recognised for its excellent health and social care research that has a positive impact on the health, wellbeing and prosperity of the people in Wales.

Strategic Aims (part 1)

To achieve our vision we will:

• ensure public involvement and engagement is central to what we do and visible in all elements of it;

• ensure our work is aligned to Welsh Government policy and has real impact;
Health and Care Research Wales
Strategic Aims (part 2)

To achieve our vision we will:

• fully integrate our infrastructure and programmes across health and social care;

• invest in areas in which Wales excels and is unique;

• increase capacity in health and social care research in Wales;

• develop systems that ensure excellent delivery and maximise the use of our resources.
Summary

• High quality research stops us making assumptions and ensures we have the **evidence** we need to deliver better care.

• Research is a **frontline service**, making a vital contribution to the improvement of the NHS and the treatments and services it delivers.

• **Health and Care Research Wales** ensures that the delivery and support for research and development in the NHS and social care in Wales enables studies to happen as quickly and efficiently as possible.
Clinical research in your department

- What clinical research activity is your team involved in?
- What clinical research are you being asked to support?
- Who is your clinical trials lead?
- Who would be your first point of contact to ask anything about a trial or patient?
- How is information communicated to the wider team?
Standards for clinical research delivery
The significance of standards

• The outcomes of research inform clinical decisions and guidance.

• If the research process is flawed, the information becomes unreliable, undermining the day-to-day practice of healthcare.

• Quality standards for the conduct of clinical research are, therefore, essential to ensure we conduct safe and meaningful studies.

• The international standard for the conduct of clinical research is Good Clinical Practice (GCP).
The Principles of GCP

The Principles of Good Clinical Practice (GCP) are at the heart of the guidance and legislation which governs the conduct of any clinical research carried out in the NHS.

There are 14 principles of GCP including...

1. The rights, safety and well-being of the trial subjects shall prevail over the interests of science and society.
2. Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks.
3. The study conducted within a trial shall be such that it may be reproduced at any time in the appropriate manner.
4. The necessary procedures to secure the quality of every aspect of the trial shall be complied with.
5. The safety of the trial subjects shall be validated by appropriate and effective monitoring and supervision.
6. Adequate arrangements shall be made to ensure the safety of the trial subjects.
7. The methods of clinical evaluation shall be such as to ensure reliability and accuracy.
8. The clinical evaluation shall be carried out in a manner which will ensure consistency in the presentation of the results.
9. All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.
The Principles of GCP

The Principles of GCP are the foundation of high quality, ethical research practice. They developed from a real need, from real cases.
Clinical Trials of Investigational Medicinal Products (CTIMPs)

- **Safety, quality and efficacy** of medicines must be demonstrated before they are authorised for use.

  - Medicines which are being investigated through a clinical trial are known as **Investigational Medicinal Products (IMPs)**.

- **Clinical Trials** of Investigational Medicinal Products (CTIMPs) are conducted to gather the evidence for a licence (marketing authorisation) to be granted, or to find out more about medicines which already have a marketing authorisation.
Clinical Trials of Investigational Medicinal Products (CTIMPs)

- Investigational Medicinal Products (IMPs) can include:
  - **Non-standard** regimens, which may be experimental
  - Standard regimens administered at **different doses** to those given in standard care (as per the licence).
- In the UK, Clinical Trials are governed by the UK Medicines for Human Use (Clinical Trials) Regulations 2004.
UK Policy Framework for Health and Social Care Research

• UK Policy Framework for Health and Social Care Research published in October, replaces the Research Governance Framework

• Sets out high-level principles and responsibilities, applicable to ALL health and social care research

• Aims to help make the UK an even better place to do research

• Updates and training will be made widely available to support implementation
Other standards

• **Overarching regulations**, for example
  
  • Human Tissue Act (2004)
  • Data Protection Act and General Data Protection Regulations (2018)
  • Human Medicines Regulations (2012)
  • Transport of dangerous good regulations

• Local NHS health board/trust **policies and procedures**

• **Professional standards**
The aim of GCP

… and all other standards which govern clinical research is to ensure:

- The rights, safety and well being of study participants are protected
- Research data are of a high quality
Summary

• Quality standards, including Good Clinical Practice (GCP), are essential to protect participants and ensure the integrity of research data.

• Guidelines and principles have been developed over time as a result of unethical and dangerous practice. In the UK these have culminated in the Medicines for Human Use (Clinical Trials) regulations.
Roles and responsibilities
Key roles
There are three key roles in the research process that provide oversight and support study conduct

• Sponsor
• Chief Investigator (CI)
• Principal Investigator (PI)

The person or people performing these roles can delegate the tasks associated with their role to others in the site team, but they always remain ultimately responsible for them.
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Site team

- A wide range of people may make up the local Site team. These may include the clinical team, pharmacy, laboratories and others.
- Staff administering the investigational medicinal product (IMP) are part of the site team.
- Research participants have given their consent to participate in research and to take the medicines prescribed in clinical trials.
Your responsibilities

- You have a responsibility to follow the instructions provided for the task you are performing
- You must be familiar with your role and trained in the relevant procedures
The study protocol

- Sets out how the research question will be answered through the conduct of the study
- States how scientific integrity and data quality are to be achieved in the study, including laboratory processes
- Helps to ensure the rights, safety and wellbeing of participants are protected
Local SOPs and Instructions

Your team’s research lead will:

• ensure there are local Standard Operating Procedures (SOPs) in place which provide instructions common activities associated with administering IMPs in anticancer treatment

• consider how the protocol will be implemented for each study, including:
  • schedule of events and activities
  • collecting study specific data and samples
  • administering the investigational medicinal product (IMP) to the participant

• ensure there are study specific instructions and proformas in place

• ensure appropriate training is provided.
Knowing your responsibilities

• You have a responsibility to follow the instructions provided through documentation and training on:

  • Local SOPs
  • Study specific instructions
  • Study specific proformas

• If you are unsure about anything in these documents, or have a question/issue that is not covered, escalate it to your clinical trials lead.

• You should also escalate any issues you feel may impact on the integrity of the data produced or the safety of participants.
Summary

- The Sponsor, Chief Investigator (CI) and Principal Investigator (PI) are responsible for ensuring the study meets all the required standards.

- Staff administering the investigational medicinal product (IMP) are part of the PI’s site team and should understand the activities they are being asked to deliver.

- There should be a research lead/champion in the team with a more detailed understanding of clinical research and who can provide advice and be the point of contact to the research team and chemotherapy staff.
Documentation and data
Collection and use of research data

• Data collected when administering the investigational medicinal product (IMP) forms part of the study data. It contributes to answering the research question and helps to ensure participants are safe.

• Study data is recorded in various records such as patient notes or dispensing records. As this is the original record, it is known as Source data.

“All information in original records and certified copies of original record of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents”

ICH GCP 1.51
Collecting high quality data

- All study data, whether handwritten or electronic, should be:
  - Accurate
  - Complete - Always provide all the data required. Blanks fields mean the data is incomplete, and the sponsor will require an explanation from the research lead as to the reason
  - Legible - It is usual to write in black ink as completed documents may be photocopied or scanned
  - Attributable - It should be clear who has completed the data
  - Timely - the data should be recorded at the time it is collected, or as close to this as possible.
Collecting high quality data: metadata

- Metadata is data that describe the attributes of other data, and provide context and meaning.

- Metadata describe the structure, data elements, interrelationships and other characteristics of data, and attribute the data to an individual.

- For example: **data** (bold text) and *metadata* (italic text)
  
enalapril, batch 1234, **2.5mg. J Smith 01/07/14**

- Metadata forms an integral part of the original record. Without metadata, the data has no meaning.
Collecting high quality data: participant initials and ID

- Participant initials and identification number must always be provided where required
- This ensures the data is associated with the right participant throughout the study
- Check local or study specific conventions for completion
Collecting high quality data: dates and numbers

• All dates and numbers should be provided where required

• Complete all the fields so it is clear all data has been provided

• Check local or study specific conventions for completion
Collecting high quality data: making changes

• If you make a mistake place a single line through the entry, and make the amendment clear.

• Initial and date any alteration, even if completing blank fields retrospectively

• Never occlude the original entry

• Never, ever use Tippex or Post-it notes

• Always document the reason for the change.
How we ensure the quality of the data

- All Sponsors must provide evidence of how they will maintain standards by monitoring and accounting for the study’s conduct

- The UK Competent Authority, the Medicines and Healthcare products Regulatory Agency (MHRA), conducts GCP Inspections for CTIMPs, which may include the review of data and systems

- Good documentation serves to demonstrate the compliance with the standards of GCP and with all applicable regulatory requirements, and therefore the quality of the research.
Summary

- Data collected when administering the investigational medicinal product (IMP), including metadata, forms part of the study data, helping to answer the research question and maintain patient safety.

- The Sponsor will monitor the quality of study data, including data related to the IMP.

- The MHRA may also inspect this data if the study is a CTIMP.
Administering IMPs
Who can administer IMPs?

- Anyone who would administer medicines as part of their job is able to administer IMPs, providing they have been trained in:
  - local SOPs
  - specific instructions for each trial
  - relevant standards of research delivery practice (for example, this course)

- These individuals should sign a ‘signature log’ for the trial to confirm they are appropriately trained and are taking on this duty.
Administering IMPs

- Informed Consent
- Randomisation
- Blinding
- Medical assessment
- Prescription filled
- Checking
- Returning/disposing of packaging

We will now explore what happens before, during and after administering IMPs, highlighting what others do and what you need to do.
Administering IMPs: Informed Consent

**Things to consider:**

- Research participants have given their consent to participate in research and to be given the IMPs prescribed in clinical trials.
- This will be documented in the patient record, along with a copy of the signed consent form.
- Ensure you are aware of your Health Board/Trust’s process for ‘flagging’ that someone is participating in clinical research.
- Escalate any queries or issues to the research nurse or your clinical research lead.
Administering IMPs: Randomisation

What is randomisation?

- In a randomised study, the participant is assigned to a particular treatment group on a random basis, to reduce selection bias.
- Processes will be in place to randomise participants to a treatment ‘arm’.
Administering IMPs: Blinding

What is blinding?

- In a **blinded** study the patient (**single blind**) and the clinical team (**double blind**) do not know which treatment group they have been assigned to, to reduce bias in the conduct of the study.

- Blinding is sometimes known as ‘masking’.

For example, a blinded trial which compares a new treatment with an existing treatment both treatments will be prepared to look, taste and be packaged in the same way to ensure they cannot be distinguished from each other.
Administering IMPs: Medical assessment

Informed Consent

Randomisation

Blinding

Medical assessment

Prescription filled

Checking

Returning/disposing of packaging

Medical assessment prior to administration of IMP

- Prior to administration of the IMP, a doctor trained in the study procedures will perform a assessment to
  - ensure the participant is still eligible for the study
  - determine the dosing of the IMP
- A clinical trial prescription is generated, following local SOPs.
Administering IMPs: Prescription filled

Prescription filled by pharmacy

- Pharmacy will have their own processes in place to make up and dispense the clinical trial prescription.

- The IMP will either
  - be delivered to the department, or
  - you should follow Health Board/Trust SOPs for collection from pharmacy.

- Escalate any queries or issues to the research nurse or your clinical research lead.

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<th>Informed Consent</th>
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Administering IMPs:
Checking

- Informed Consent
- Randomisation
- Blinding
- Medical assessment
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- Returning/disposing of packaging

Things to consider:

- Follow your Health Board/Trust procedures for checking medicines prior to administration
- IMPs are sometimes labelled differently to other medicines
  - The name of the participant may not be included - a patient ID or randomisation code used instead
  - If the trial is blinded, it may not be clear what the IMP being dispensed is - this will be covered by your Health Board/Trust’s medicines administration/management policy
- Escalate any queries or issues to the research nurse or your clinical research lead.
Administering IMPs:
Checking

Things to consider:

- The information you are checking against is sometimes different in a clinical trial
- A schedule of events for the trial will be provided in the patient record/department notes, including:
  - Study name and identification number
  - Patient identification number
  - Any randomisation codes, or details of which treatment arm they are randomised to (if not blinded)
  - Treatment required at the specific trial visit
- Escalate any queries or issues to the research nurse or your clinical research lead.
Administering IMPs: Checking

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<th>Step</th>
<th>Details</th>
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<tr>
<td>Informed Consent</td>
<td>Specific instructions for dosing or administration of the IMP may be included in the clinical trial prescription or label</td>
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<tr>
<td>Randomisation</td>
<td>There may also be specific instructions or proforma detailing how to deliver the IMP in the patient record/department notes</td>
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<tr>
<td>Blinding</td>
<td>These may also detail additional data collection requirements, such as recording start/stop times and additional observations or tests</td>
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<tr>
<td>Medical assessment</td>
<td>Remember that these are source data</td>
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Adverse Events

- An **Adverse Event (AE)** is any untoward medical occurrence which happens during a study
  - Adverse events do not have to appear to be related to the study medication or procedures to be relevant
  - Sometimes it is only when data from a very large number of people is collated together that patterns emerge showing the medicine is resulting in unexpected reactions.

- If a trial participant has an adverse event before, during or after administration of the IMP it is important that you:
  - Ensure their safety and wellbeing
  - Document *everything* fully
  - Escalate the event to a research nurse or doctor involved in the trial while you are still on duty.
Administering IMPs: Returning/discardng packaging

Things to consider:

- Packaging and any unused IMP is usually returned to pharmacy.
- You may sometimes be required to dispose of packaging (e.g., chemotherapy).
- Ensure you follow any Health Board/Trust SOPs or trial specific instructions/proformas, including documentation requirements.
- Escalate any queries or issues to the research nurse or your clinical research lead.
Session complete!

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- Practice standards
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