INTRODUCTION

“It’s some kind of research, isn’t it?”, . . . “experiments with drugs” or worse “using human as guinea pigs!” Thus run the responses when I first mention my current post of oncology clinical trials co-ordinator. Therefore in this article I will describe the general process of conducting clinical trials and acquaint you with the local situation regarding the trials that are in progress.

Clinical trials are now a well established method of testing the benefit of a new drug or treatment against the standard. They have a crucial role in the development of new cancer drug treatments and also enable the reevaluation of standard therapies. They are defined as “a scientific experiment designed to answer a clinical question”, and can also assess morbidity and toxicity, test a biological hypothesis and help estimate the cost benefit of a treatment.

A HISTORICAL BASIS

Perhaps the first reported controlled clinical trial is the study of the treatment of scurvy by James Lind in 1747[2]: “Their cases were as similar as I could have them . . . they lay together in one place . . . and had one diet common to all”. Two patients were each treated with six different treatments: cider, vinegar, sea water, elixir vitriol, oranges, lemons and nutmeg. Lind recorded in great detail the subjects, the treatments and clinical outcomes of each patient and observed “the most sudden and visible effects (from) the oranges and lemons” with one (patient) returning to duty and the other caring for the rest of the sick.

Unfortunately the small size of the trial raised doubts about the improvements seen and the trial was not repeated to confirm the results. It was another fifty years before the use of lemon juice became standard in the Royal Navy[3].

This landmark study illustrates a number of principles of the clinical trial:-

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* Production of commercial-sized batches

1. The same condition for the patients apart from the therapies under comparison.
2. Controlled comparison of similar cases.
3. Detailed recording of treatments and events.

The beginning of the modern clinical trial was marked by the large-scale randomised trial of streptomycin treatment in tuberculosis conducted by the British Medical Research Council in 1948. There has been a large growth in clinical trials since that time, particularly in cancer, due to the development of many new cancer therapies.

NEW DRUG DEVELOPMENT

In the twentieth century we have come to expect and demand safety and an almost complete lack of toxicity for the ever-increasing variety of drugs we consume. The development of a new drug is a complex and lengthy business and can take fourteen years or more (see Fig 1).

PHASES OF DEVELOPMENT

The phases of clinical trials have been used in the pharmaceutical industry in the development of new drugs but can also refer to non-drug treatments.

Phase I trials – are concerned primarily with evaluating drug safety and assessing toxic effects of treatment, in non-patient healthy volunteers. They also identify which dose is optimal for use in phase II trials.

Phase II trials – are the first patient trials using a limited number of subjects. They test the efficacy of a new drug, provide further toxicity information and are usually limited to a few hundred patients.

Phase III trials – involve larger patient groups with the purpose of determining the short and long term
safety/efficacy balance of a drug, as well as assessing its overall and relative therapeutic value. Generally the circumstances of these trials should be as close as possible to normal conditions of use.

**Phase IV trials** – continue the monitoring of a new drug, after it has received a product licence and is marketed. They serve to establish the general usefulness of a new drug used in normal clinical practice in a significant number of patients.

**Named patient** – this mechanism is employed when an unlicensed drug can be supplied to a doctor for the treatment of a particular (named) patient. Pharmaceutical companies are usually sympathetic to these requests, particularly where no alternative therapy is available, but the patient must be carefully monitored and a report submitted to the company.

**REGULATION OF DRUG RESEARCH**

In the UK, since the Medicines Act 1968, drug licensing is handled by the Department of Health. The licensing authority can issue a Clinical Trials Certificate (CTC), manufacturing licence and Product Licence (PL). Clinical trials in patients should be covered by a CTC or a PL but since 1981 can be conducted under the Clinical Trial Certificate Exemption (CTX) scheme whereby a summary of the pre-clinical data and the trial protocol are submitted to the Medicines Control Agency (MCA). If the data is acceptable a CTX will be granted within 35 days. If the submission is rejected the company must apply for a full CTC which may take many months.

**TRIAL DESIGN & PROTOCOLS**

Clinical trials may be designed by a medical adviser or clinical research assistant (CRA) within a pharmaceutical company medical department. Alternatively the design may be proposed by a doctor or a medical group who may then approach the drug company asking for supplies of a new treatment.

The design of the trial is a description of the way patients will be studied, in terms of selection, treatment and assessment.

**Uncontrolled** – where all patients receive the same therapy. This may be useful in screening for new treatments (phase I) but is limited in identifying optimal standard treatment and is most subject to bias.

**Historical Control** – compares a group of patients treated with a new treatment with an earlier series of patients (usually at the same unit) treated with the previous standard therapy.

**Concurrent Control** – compares two or more treatments in patient groups over the same period of time. By using concurrent controls, differences in ancillary care or changes in methods of staging and outcome, assessment can be minimised.

**Randomised Controlled** – provides the best protection against bias by randomly allocating patients to receive the treatment or control. This ensures that differences in response between groups can be attributed to the treatments under study rather than to particular characteristics of the patient groups.

Cross-over trials – comparing the effect of one treatment after another on the same individual.

An essential feature of a clinical trial is that it is a prospective study examining specific hypotheses. Hence it is important that the trial is properly planned and the details clearly set out in a signed protocol (see Table 1)."
not be offered any inducements or payments to participate in a clinical trial although travelling expenses should be met. The trial drugs should be provided free of charge.

If patients agree to participate in the trial they usually sign a consent form which is countersigned by the clinician and the form is kept in their hospital/GP notes. These notes should also identify which patients are participating in a clinical trial.

**DATA COLLECTING & MONITORING**

At the end of a clinical trial, after possibly several years of work, the only tangible product is a collection of pieces of paper called a case report form (CRF). This is where the information and results of a trial are recorded.

It is the responsibility of the Trial Investigator (usually the senior clinician involved) to ensure that the CRF is complete and signed accordingly. The CRFs are usually checked and monitored on site by the clinical research assistant of the drug company and then one copy is given to the investigator and the originals are forwarded to company's data management department for analysis.

Once the whole study is completed, the original CRFs will be archived by the drug company for fifteen years or the lifetime of the product. The investigator must retain a register of the identification of trial patients and their casenotes also for fifteen years.

**THE CURRENT LOCAL SITUATION IN ONCOLOGY CLINICAL TRIALS**

As the clinical trials co-ordinator and data manager for the Oncology Department, I am responsible for all aspects of oncology clinical trials, reporting directly to the consultant medical oncologist, Dr Malcolm McIlmurray, who is the Principal Investigator in all the trials.

My duties cover the following areas:

- Inaugurating a trial specified by Dr McIlmurray. This involves liaison with the CRAs of the company or MRC, perusing the protocol, obtaining information and consent forms and agreeing the funding required, including indemnity cover. This can take many weeks.
- Submitting applications to the health authority ethics committee and being available to discuss areas of concern.
- Following up the patients after their initial consultation with Dr McIlmurray. This usually occurs a few days after their appointment and I visit them at home allowing sufficient time for informed consent to be obtained.
- Thereafter I ensure strict adherence to the protocol in terms of investigations and treatment. This involves close liaison with all patients and staff undertaking patient care, and being available for monitoring visits from the company CRAs. Also I report any serious adverse events to the appropriate authorities.
- Liaising with pharmacy staff regarding drug availability and assisting with monitoring of drug compliance.
- Completing the CRFs accurately and maintaining the quality standard.
- Being available to advise and assist local nurses, GPs and hospital doctors on most aspects of clinical trials.

The following clinical trials are currently being undertaken by the Oncology Department of the Royal Lancaster Infirmary.

**QUASAR** – A United Kingdom Co-ordinating Committee of Cancer Research (UKCCR) study of Dukes “C” colorectal cancer

**ABC** – A UKCCR randomised trial of adjuvant endocrine therapy, chemotherapy and/or ovarian suppression on women with early breast cancer.

**LIGLA** – A Scotia Pharmaceuticals randomised controlled 3 arm parallel study to assess the effect of Lithium-GLA (LiGLA) in patients with pancreatic cancer.

**RE02** – An MRC trial of pre-operative chemotherapy for cancer of the oesophagus.


**GEMCITABINE** – An Eli Lily phase III randomised trial comparing Gemcitabine + Best Supportive Care with Best Supportive Care alone in advanced non-small cell lung cancer.

**IFOSFAMIDE & EPIRUBICIN** – An Asta Medica phase IV randomised study comparing Ifosfamide and Epirubicin in patients with relapsed metastatic breast cancer.

**BA07** – An MRC randomised phase IV trial of Methotrexate and Vinblastin (MV) vs Cisplatin, Methotrexate and Vinblastin (CMV) in advanced transitional cell cancer of the bladder.

**ICON 1 & 2** – An MRC study of chemotherapy in early and advanced ovarian cancer.

**EXEMESTANE** – A Pharmacia phase III trial assessing the antitumour efficacy of exemestane in post-menopausal patients with metastatic breast cancer, failing on non-steroidal aromatase inhibitors.

**CLL 3A** – An MRC study of symptomatic vs non symptomatic treatment of chronic lymphatic leukaemia.

**REFERENCES**

2. Lind J. A treatise of the scurvy. In three parts containing an enquiry into the nature, causes and cure of that disease. Sands Murray and Cochran, Edinburgh 1753.

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