



Clinical Trials

Royal Irish Academy | Expert Statement



Introduction

Clinical trials and studies are conducted in order to ascertain the safety and/or efficacy of therapeutic interventions, and to generate evidence on the benefits and harms of these. Approval must be obtained from an ethics research committee before any clinical trials can be carried out. Ethics research committees are composed of lay and health care professionals who review the trial protocol, the suitability of the investigator(s), facilities, and the methods and materials to be used in obtaining and documenting informed consent of the trial subjects. These committees may also interview the principal investigator(s) as part of the review and approval process.

In the context of medicinal product trials being conducted at multiple sites, under the clinical trials legislation a sponsor need only seek ethical approval from one of the twelve recognised ethics committees regulated by the Minister for Health. However, this is not the case for multi-centre trials which do not involve investigational medicinal products (e.g. translational or radiotherapy trials) where approval of the relevant ethics committees is required for each centre. The Department of Health has committed to establish a national ethics committee to speed up and streamline the process for these trials, but this has not yet happened.

Good clinical practice

A clinical trial must be conducted in accordance with good clinical practice (GCP) guidelines. Clinical trials involving investigational medicinal products are regularly inspected by the Health Products Regulatory Authority.^{1, 2, 3} These regulations protect the safety and well-being of the study participants and provide assurance that the evidence generated is reliable.

However, there is criticism that the GCP guidelines are applied too rigorously to all clinical trials and may not be necessary for non-registration trials, non-intervention studies and non-pharmacological interventions. Overinterpretation of the guidelines leads to extensive and costly checking of source documentation, despite the fact that it offers little evidence that it detects errors or improves quality.⁴ Central statistical monitoring of data with targeted on-site monitoring is a more efficient and effective way of detecting errors.

Large volumes of unnecessary data on minor side effects are generated with reports to regulatory authorities, ethics committees and investigators. Although rigorous assessment is necessary in early phase clinical trials, in later phase trials all non-serious adverse events need not be communicated, as these may detract from serious reported side effects.

Serious or unexpected side effects should only be expedited if they occur in patients that have been allocated drugs used in active studies. Adverse events need to be compared collectively between study arms. This is best carried out by a data monitoring committee (DMC) independent of those conducting the study to protect the integrity of the trial.

Patient registries and electronic patient records

Access to the results of clinical trials have been achieved through the use of registries. Access to patient-level data offers investigators the opportunity for novel analysis or subset benefit of new drugs. This information, however, is not always forthcoming. The importance of conducting well-designed clinical trials needs to be

¹ EU no. 536/2014, article 2, clause 2<30> (applicable in 2019): https://ec.europa.eu/health/human-use/clinical-trials_en#rlctd

² ICH GCP E6 (EMA/CHMP/ICH/135/1995): http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf

³ EU Directive 2001/20/EC: <http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:02001L0020-20090807&from=EN>

⁴ Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials; *Therapeutic Innovation & Regulatory Science*, November 2014; vol. 48, 6: pp. 671–680., first published on October 9, 2014

conveyed to patients, doctors and policy makers, and should be part of the medical curriculum.

The results of well-conducted clinical trials are key to treatment guidelines proposed by learned societies. However, there are limitations to clinical trials. Entry criteria for trials are stringent and many patients are ineligible for inclusion based on age, co-morbidity, previous medication and other factors.

Comprehensive data collection would be enabled by an electronic patient records registry that would monitor the efficacy of trial interventions and record unexpected long-term effects. Thus, patient registries need to be created and supported longitudinally to allow this to happen.

As a first step, registries for patients with defined diseases need to be created and supported. These registries can cross borders, which is relevant for rare disease, and would provide the infrastructure for patient-centred, affordable and real-life testing of new and repositioned treatment strategies.

Patient involvement

Patients need to be informed of the value of clinical trials and involved in their design, conduct and ultimate dissemination. Involving patients in an advisory, consultative or collaborative capacity does not require specific ethical approval. Furthermore, involving patients in such a capacity provides insight into more than just the scientific effect or results of a specific treatment; it also highlights how to improve quality of life during a specific treatment.

In addition, management of the patient's condition may require a combination of treatments, varying doses and duration of treatment, as well as ancillary interventions which require evaluation in trials. Modern technology of imaging, gene-sequencing and identifying molecular markers help to identify patients that might respond to one or another form of treatment. Patients with cancer, for example, whose tumours can be characterised

phenotypically and genotypically, may seek a clinical trial that targets their patient or tumour profile.

Thus, a more patient-centred approach, that considers the needs and values of the individual, and places the patient as the key stakeholder in the research process, is a shift that should be embraced within the clinical trials arena.

European perspective

Clinical trials by necessity extend beyond national borders, so that sufficient number of patients can be recruited. Investigators need approval and funding at both a local and a European level. At the moment, this is cumbersome as at least three different European Commission Directorates are involved.

The current legal framework for health research is developed by trials (DG Sante), data-protection (DG Justice) and invitro investigation (DG Grow); this could be simplified if a single application could satisfy all three.

Economy

It is important that Ireland remains competitive in clinical trials. A key performance indicator for teaching university hospitals should be a percentage of patients undergoing treatments who participate in clinical trials. An independent report for Cancer Trials Ireland estimates that in 2016, 3.63 million euro of Health Research Board and Irish Cancer Society funding (public) saved the HSE 6.5 million euro in cancer drug costs, generated almost 6 million euro in tax revenues and contributed 16.5 million euro to Ireland's GDP and supports 230 jobs mostly high-quality positions.

Cancer Trials Ireland generated 3.85 million euro to fund international studies. Overall health research funding has been on a downward trend and Ireland has a low ratio of investment in Health Research to GDP. It is difficult to estimate voluntary bodies contributions to clinical trials, but investigators have found funding to be increasingly challenging.

Recommendations

- Increase patient awareness of the value of clinical trials
- Develop patient-centred clinical trials
- Develop a streamlined process for ethical review of clinical trial protocols⁵
- Develop and maintain registries that phenotypically, genotypically and molecularly describe patients
- Clinical trials should become part of the care pathway in Irish hospitals
- Simplify procedures for developing clinical trials
- Simplify applications for EU funding
- Participation in clinical trials is a key performance indicator for university teaching hospitals

⁵ DKM-Economic-Impact-of-Cancer-Research-Final-Report

