Paediatric and Perinatal Drug Therapy, 2007; 8 (3)

Maintaining good clinical research practices in paediatric studies

Carl Naraynassamy

The Association of Clinical Research Professionals, Windsor, UK

Corresponding author

Carl Naraynassamy, The Association of Clinical Research Professionals, Goswell House, Windsor, SL4 1DS, UK.
Email: carln@acrpnet.org

For many years, drug studies in children were shunned by researchers. Today, paediatric studies are considered acceptable and are also mandated by the law. The law in Europe further stipulates that all clinical studies whether intended for regulatory authority registration or performed for academic purposes must conform to Good Clinical Practice (GCP). This article discusses GCP in terms of its origins, principal tenets, the duties of clinical researchers, the additional considerations for paediatric studies, the need for adherence and the penalties for non-compliance as well as the help that researchers may receive in order to remain compliant.

Paed Perinat Drug Ther 2007; 8: 131–133

Keywords: Good Clinical Practice – paediatric studies – non-compliance – European paediatric regulation – monitoring – inspections

Introduction

Paediatric studies were once shunned but increasing studies are being performed; thus under the 2003 US Pediatric Research Equity Act (PREA), all US biopharmaceutical companies have to test new drugs for safety, efficacy and dosing information in children[1]. The 2006 European Regulation[2] on medicinal products for paediatric use, which came into effect on 26 January 2007, imposes similar obligations on pharmaceutical manufacturers in the European Union. The guidance document on clinical investigation on medicinal products in paediatric populations E11 by the International Conference on Harmonisation (ICH) recognises five categories of children[3]:

- preterm neonates
- full-term neonates
- infants and toddlers
- children
- adolescents

The number of studies performed may therefore increase even further if the European regulators demand paediatric studies in more than one age group. The European Directive 2001/20/EC also introduced the requirement that academic studies would, like commercial studies, need to conform to Good Clinical Practice (GCP)[4].

Good clinical research practices

It has been the rule for many years now that clinical studies used to support the licensing of medications are performed according to GCP. Regulatory authorities will withhold granting a licence if there is evidence that the collection of the supporting data was achieved in violation of GCP. GCP refers to the international standard of designing, conducting, recording and reporting clinical studies so that the rights, safety and well being of the study subjects and the integrity of the data are protected. These principles are contained in the ICH Technical Requirements document E6 on GCP[5] and have

their origins in the Declaration of Helsinki of 1964[6]. This ICH guideline was originally developed for investigational medicinal products intended for registration in the EU, USA, and Japan. The World Health Organization (WHO) has also published a handbook of GCP where it enunciates 14 principles of GCP. The WHO states that the responsibility for GCP is shared by those involved in the clinical research enterprise and this includes sponsors, investigators and their research personnel, Clinical Research Organisations (CROs), Ethics Committees, Regulatory Authorities and subjects.

There are 13 principles of ICH GCP. These are:

- The need to conduct studies according to the ethical principles which originate from the Declaration of Helsinki, according to GCP and the applicable laws.
- Studies should begin (and continue) only if the expected benefits for the subject and society justify the risks.
- The most important considerations in a study are the subjects' rights, safety and well being.
- A study should be supported by the availability of adequate clinical and non-clinical information.
- Studies must be scientifically sound, and described in a clear detailed protocol.
- Studies must comply with the protocol which will have received prior favourable opinion by an ethics committee.
- Medical care and medical decisions taken on behalf of subjects are the responsibility of physicians.
- All study personnel should be qualified by education, training, and experience to perform the tasks that they undertake.
- Subjects must give free informed consent prior to their participation.
- The manner that study information is recorded, handled and stored must allow their accurate reporting, interpretation and verification.
- The identity of subjects must be kept confidential.
- Investigational products must be manufactured, handled and stored according to the principles of Good Manufacturing Practice and must be used according to the protocol.
- There must be quality assurance systems in place.

Those undertaking paediatric studies need to subscribe to these GCP principles in addition to any applicable international or local rules which govern research in this population, e.g. ICH Guidelines E11.

Compliance and the penalties attached to non-compliance

Research teams and those involved with research with humans must ensure that they comply with GCP. They must remain vigilant since the standards required for the observance of GCP evolve. For example, the European Directive 2001/20/EC introduced a requirement for ethics committees which lacked expertise in paediatrics to seek advice when addressing clinical, ethical and psychosocial problems and another requirement for academic sites to ensure that the studies that they sponsored were monitored. This recent stipulation is posing a challenge to academic centres as a recent survey in the UK shows that half of the centres do not yet have a monitoring system, very few personnel are trained in monitoring and where monitoring happens, this is infrequent[7]. Academic sites performing non-commercial studies are not exempt from regulatory inspections and in fact this is on the increase.

The UK Medicines and Healthcare Products Regulatory Agency (MHRA) report that, as of September 2007, they had performed routine systems inspections on eight academic sites and that 41% of the findings made were judged critical. This value is three times superior to that observed in equivalent inspections of commercial sponsors. The MHRA also report that the most common findings related to issues of subject confidentiality, pharmacovigilance and failures of record keeping. They further report that these findings would not have been made if adequate monitoring and auditing procedures had been put in place[8]. It is submitted that academic centres need to monitor the studies that they sponsor as stringently as the pharmaceutical industry does for its own and will need to put adequate resources to this effect. Invoking inadequate resources for not complying with the law cannot constitute an inadequate justification.

Non-compliance with GCP may have serious consequences for the clinical researchers and their institutions. In 2001, on the basis of findings made on investigating the death of a study subject, the US Office of Health Research Protection took the unprecedented decision of closing the research activities funded by the public purse at the world renowned John Hopkins University[9]. At the time of closure there were some 2400 studies ongoing. Both the ethics committee and the investigators were blamed; the former for not performing an adequate review of studies, e.g. not securing from the investigators adequate information on the investigational medicinal product, and the latter for failing to disclose the extent of risks to the subject.

In 2006, the UK General Medical Council (GMC) found a research physician guilty of serious

professional misconduct because he demonstrably failed to perform necessary examinations on the subjects and to train his research nurse adequately in her role. He was also found not to have acted as somebody who had ultimate responsibility for that trial[10]. For the misconduct the GMC imposed conditions on his registration as a doctor.

Researchers should also note that clinical research activities are not exempt from litigation. The most discussed one recently and still *sub-judice* is TGN 1412 study where a number of volunteers claim to have suffered injury as a result of taking part in this Phase 1 study[11]. Researchers should further note that inadequate compliance to GCP can hurt professional reputation[12]. This is even more critical with the increasing competition for research funds by centres from outside the traditional research territories.

It is undeniable that there are costs attached to the observance of GCP. These costs must however, not be seen as external and additional to the research process, but as inherent to it. Equally, GCP must not be observed for the purpose of being seen to comply or pass the test of the monitor and auditor. Researchers must cultivate conscience and responsibility rather than adopt a culture of compliance[13]. The observance of GCP also needs to be read in the context of the opportunities offered. Any researcher or research team operating in a growing sector, and confronted with the needs to work to stricter conditions, will be able to raise their skills, especially project management and resource management. Monitors and auditors, whether internal or external to the researcher's organisation, should be viewed as allies who can offer knowledge and skills rather than policemen. GCP must not be thought to be divorced from other standards and practices deemed essential for good research like financial accountability, good personnel management, mentoring and training and leadership.

Guidance for researchers

Since clinicians and other clinical personnel are not typically formally trained on how to conduct clinical studies, they will often give inadequate consideration to GCP. Sometimes GCP is dismissed as a bureaucratic hindrance. In many countries, ethics committees seek to receive confirmation that a researcher is trained in GCP. Investigators who need training in GCP should therefore consult with their Ethics Committees and alternatively look for the various courses run by academic institutions, the pharmaceutical industry, some paediatric research networks or the non-profit organisations. Investigators and their staff can today take examinations which will test their competency in GCP and these are run by organisations like the Royal Colleges of Physicians and The Association of Clinical Research Professionals. In the current climate of increased transparency and evidence based pronouncements, GCP which protects the study subject and the quality of the data is an essential component of the research process in paediatric populations.

References

1. Food and Drug Administration. Pediatric Research Equity Act 2003. (www.fda.gov/opacom/laws/prea).
2. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (Official Journal L378,27/12/2006 p1-19).
3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (Topic E11) Clinical Investigation of Medicinal Products in the Paediatric Population. CPMP/ICH/2711/99.
4. Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws regulations and administrative provisions of the member states relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use.
5. International Conference on Harmonisation of Technical Requirements Guidance on Good Clinical Practice (Topic E6) (CPMP/ICH/135/95).
6. World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects, 2004.
7. Association of Clinical Research Professionals. Survey of monitoring practices in the UK non commercial sector, 2007 (In preparation).
8. Medicines and Healthcare Regulatory Agency. Next steps in Good Clinical Practice for non-commercials symposium on 24 September 2007, York, UK.
9. Alliance for Human Research Protection. OHRP suspends John Hopkins Research Licence for Federal Funded Research, 2001.
10. General Medical Council. Report of the fitness to practise panel in the case of Dr Richard Wilson, 17 October 2006 (www.gmc-uk.org).
11. Medicines and Healthcare Regulatory Agency. Investigations into adverse incidents during clinical trials of TGN 1412, 2006 (www.mhra.gov.uk).
12. Tiner R. Academia and industry; can we work together? Presentation given at the 5th International Workshop on Paediatric Clinical Trials, 18-19 June 2007, Derby, UK.
13. Association of American Medical Colleges. Statement on protecting human subjects in research: are current safeguards adequate? Submitted to the Committee on Health, Education, Labor and Pensions on 23 April 2002.

CrossRefs are available in the online published version of this paper:
http://www.librapharm.com
Paper PPDT-0200_2, *Accepted for publication:* 13 December 2007
Published Online: 11 January 2008
doi:10.1185/146300908X254152