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Complying with the European Clinical Trials directive while surviving the administrative pressure – An alternative approach to toxicity registration in a cancer trial

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Abstract The European Clinical Trials Directive of 2004 has increased the amount of paper work and reduced the number of initiated clinical trials. Particularly multinational trials have been delayed. To meet this challenge we developed a novel, simplified, fast and easy strategy for on-line toxicity registration for patients treated according to the Nordic/Baltic acute lymphoblastic leukaemia protocol, NOPHO ALL 2008, for children and young adults, including three randomisations. We used a risk-assessment based approach, avoiding reporting of expected adverse events and instead concentrating on 20 well-known serious, but rarer events

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with focus on changes in therapy introduced in the treatment protocol. This toxicity registration strategy was approved by the relevant regulatory authorities in all seven countries involved, as compliant within the EU directive of 2004. The centre compliance to registration was excellent with 98.9% of all patients being registered within 5 weeks from the requested quarterly registration. Currently, four toxicities (thrombosis, fungal infections, pancreatitis and allergic reactions) have been chosen for further detailed exploration due to the cumulative fraction of patients with positive registrations exceeding 5%.

This toxicity registration offers real-time toxicity profiles of the total study cohort and provides early warnings of specific toxicities that require further investigation.

1. Introduction

Since the implementation of the European Clinical Trials Directive (2001/20/EC) (ECTD) [1] in May 2004, clinical trials have been challenged by increasing requirements for documentation and good clinical practice (GCP) monitoring. Although the initial analyses of the impact of the European Clinical Trials Directive did not indicate a decrease in the number of registered, investigator-initiated clinical trials [2], the general experience has been that the directive has led to delays in the opening of academic trials [3–6], and even a fall in number of applications [7]. Furthermore, the intended harmonisation of the national requirements for clinical trials in Europe has not been accomplished, and member states differ in terms of demands on the level of GCP monitoring, the level of reporting of Adverse and Serious Adverse Events, insurance requirements and sponsor responsibilities [8]. So far, there is no evidence that patient safety has increased as a result of the ECTD. This paper illustrates some of the existing possibilities within the current ECTD in some member states, particularly the possibility of not reporting well-known adverse events (AEs) while maintaining a high level of security surveillance of the trial.

The improved overall survival rates of childhood cancer is likely to be the result of systematic entry of patients into multi-centre clinical trials [9], many of which have been organised as comprehensive treatment protocols with the majority of patients taking part in controlled studies [10–13]. The improvement in cure rates has in general been achieved with drugs available for decades. Nevertheless, childhood cancer trials are in the vast majority of European countries still burdened by demands for detailed registration not only of suspected unexpected serious adverse reactions (SUSARs) but also of well-known AEs and serious adverse events (SAEs) occurring in most, if not all, patients. Yet, such toxicity data are rarely, if ever, published, since they are well known by clinicians and have previously been reported.

The ECTD has, so far, been implemented by most national medicines agencies with requirements for all interventional trials, regardless of the level of risk to the patients and whether the study in question is investigator-driven or sponsored by the pharmaceutical industry, and regardless of whether the study addresses a well known Investigational Medicinal Product (IMP) or a new drug. Registration of toxicities is at risk of being incomplete, since such registrations are resource consuming and, apart from SUSARs and SAEs, adds little to what is already known. Finally, for non-fatal toxicities such as thrombosis, organ failure or neurotoxicity, the long-term sequelae are at least as important as the fact that the specific toxicity occurred, but the latter is rarely reported. In addition to these difficulties there is a non-uniform interpretation of the Clinical Trial Directive across the EU member states medicines agencies, making multinational clinical trials unnecessarily difficult to implement and carry out. It is, so far, unclear whether the newly introduced Voluntary Harmonisation Procedure (VHP) will reduce these problems, but the first reports on the experiences with VHP seem promising [14–16]. In addition, the new proposal for a Regulation on Clinical Trials on medicinal products has now been presented. The proposal seeks to reduce the burden of bureaucracy while preserving patient safety [7]. The new proposal will become law rather than a directive, thus, hopefully, avoiding differences in interpretations within countries. In addition the proposal will introduce proportionate regulatory requirements accepting significant differences in potential risks to patients, meaning a clinical trial such as the one presented in this paper would become a lower risk trial, with no new agents, comparing well known therapeutic strategies inducing only well known and common (including severe) toxicities [17,18].

To address the needs for extensive, prospective, toxicity registration in investigator-initiated clinical trials and to minimise the burden of registration for the local clinicians, while still complying with the requirements of the ECTD and the National Medicines Agencies, we developed a novel toxicity registration strategy and a user-friendly on-line registration platform for the NOPHO ALL2008 acute lymphoblastic leukaemia (ALL) protocol. The approach takes into account the prior knowledge and experience of well known IMPs, thus using a risk-assessment based approach for monitoring only selected serious adverse events in the assessment of serious toxicity by the use of these drugs.