admission he was found to be profoundly neutropenic with a total white cell count of 0.4 and no neutrophils seen on a blood film. He was also thrombocytopaenic with a nadir platelet count of 7×10^9/l. He was treated with intravenous broad spectrum antibiotics and platelet transfusion. Serial blood cultures and urine culture failed to detect a causative organism but his condition improved with recovery of haematological indices by day 17.

At cycle 2 the total dose of all agents was reduced by 10% and severe neutropenia was avoided. A repeat CT scan of abdomen and pelvis on the day prior to the planned start of cycle 3 showed complete resolution of the pelvic lymphadenopathy and therefore it was decided to give another two cycles of ICE. Cycle 3 was again complicated by an episode of neutropenic septicaemia, and thrombocytopaenia requiring admission and administration of intravenous antibiotics and platelets. As before, no organism was identified on bacteriological investigation. Accordingly, for the fourth and final cycle of chemotherapy the total doses of drugs were reduced by a further 10%.

A CT scan 1 month after completion of chemotherapy revealed no abnormality in the pelvis and confirmed resolution of the previously noted lymphadenopathy. A repeat cystoscopy was performed and showed no evidence of residual tumour within the bladder. Bimanual examination was also normal.

In view of this encouraging response to chemotherapy he went on to receive consolidation radiotherapy at a dose of 4500 cGy in 20 fractions as a four field technique to the bladder itself. It was felt that treatment of the whole pelvis (that is the potential lymph node bearing area) was not feasible in view of the need to minimise radiation reaction of the bowel and skin. He did develop some diarrhoea but this settled on codeine phosphate.

He completed therapy 2 months ago and is currently well at home and has returned to full-time occupation.

DISCUSSION

Tumours with the histological appearance of carcinoma of the bronchus can arise in other organs. In this patient it seems unlikely in view of the non-smoking history and normal chest X-ray and CT that the bladder tumour was a metastatic manifestation of a bronchial tumour. It is of some interest that he initially had biochemical disturbances in keeping with inappropriate antidiuretic hormone production. Although we chose not to investigate this further it did resolve with effective antitumour therapy which is strong circumstantial evidence that the tumour was producing ectopic antidiuretic hormone. The prevalence of ectopic hormone production in this tumour and in small cell carcinoma of the prostate [4] suggests that these tumours derive from neuroendocrine or amine precursor uptake and decarboxylation (APUD) cells, but as in small cell lung cancer, the precise cellular derivation is uncertain.

Our ICE protocol for small cell lung cancer is known to be effective in inducing remissions in a high percentage of patients with that disease, but is also associated with profound myelosuppression. As expected we did encounter some problems in this respect with this patient, which proved to compromise the dose intensity of chemotherapy that we could actually deliver. One could argue that haematological support using granulocyte colony stimulating factor (CSF) or granulocyte/macrophage CSF may have been appropriate. Despite this reduction in planned chemotherapy dose he did achieve a complete response as judged by CT imaging and cytoscopy with examination under anaesthetic. His tetraplegic state also compromised the ideal treatment volume for consolidation radiotherapy. The (scarce) literature on small cell bladder carcinoma suggests that this is an aggressive tumour not unlike small cell lung cancer in biological behaviour. We could find only one other report of combined radiotherapy and chemotherapy in this disease. In this report patients receiving the combined approach survived longer than those not treated in this manner (78% died at mean follow-up time of 9.4 months). It, therefore, appears that combination chemotherapy may be of benefit in this rare tumour type [5].

Small cell carcinoma of the prostate is a more common entity with similar biology which responds to multi-agent chemotherapy but because of generally late and abnormal presentation carries a very poor prognosis [6].

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Towards an International Register of Cancer Trials: The UKCCCR Register of U.K. Trials

INTRODUCTION

THE UNITED KINGDOM Coordinating Committee on Cancer Research (UKCCCR) is currently developing the UKCCCR Register of U.K. Cancer Trials, covering all phase II and phase III randomised trials. The register is stored as a computer data base that will be made available to clinicians for interactive access [1]. Other European countries are planning to develop similar registers, and the UKCCCR register is expected to become an integral part of the European register of cancer trials that has been proposed under the auspices of the

European Computerized Oncology Data Exchange (EuroCODE) project.

This paper reviews the reasons for constructing registers of trials. Many aspects of the importance of registers have been described in articles published in specialised statistical or clinical trials journals [2–5] and this paper is intended to complement these more general papers and demonstrate the relevance of a register of trials in the area of cancer. We also describe the UKCCCR register and its relationship to EuroCODE and the U.S. physician data query (PDQ) database of cancer clinical trials; a more technical description of the UKCCCR Register may be found in reference [1].

THE NEED FOR A REGISTER OF TRIALS

Increasing patient accrual to trials

Registers offer an easy means for clinicians and investigators to discover the existence of trials in their area of interest, and enable them to read brief descriptions of the trials. Thus clinicians may use a register to obtain up-to-date information about new treatments being investigated and the active trials that are assessing their efficacy. If a trial seems interesting, the clinician can consider becoming a participant and can enquire about obtaining a full protocol from the trial coordinator.

At present only a small proportion of eligible patients are entered into trials; previous estimates have suggested from 1 to 3% of bowel or breast cancer patients [6] and 1 to 9% of solid tumours in general [7] were entered, and there is little to suggest those figures may have improved. Since so few patients are admitted to clinical trials, it is not surprising that many trials have problems of patient accrual.

Few types of cancer can be treated with complete success and without employing treatments that have toxic side-effects, and thus new treatments are continually being proposed. Arguably, in this situation a clinician can never remain in the state of being certain what is the best treatment, and therefore the principle "if uncertain, randomise" should apply wherever a trial exists which compares the current "standard" treatment with a new, as yet unproven but promising, treatment. If a suitable trial exists and is not contrary to the patient's best interests, the clinician should give reasonable consideration as to whether the patient might be entered into the trial. In that way the patient can receive the best available therapy whilst also helping to provide scientific information for treatment of future patients. Registers of trials ensure that lack of knowledge of appropriate trials cannot be a ground for failing to enter suitable patients into clinical trials.

Planning of studies

Those planning new trials can discover who has conducted, or is conducting, similar work or has registered an intention to do so; it is then possible to design the new trial with the maximum available information about past, present and future trials, or to consider active collaboration with another group. This ability to review current and past research activity in a disease or treatment area can be of help both to investigators and also to funding agencies. In particular, the awareness of other trials may lead to significant changes in a protocol under design, and sometimes may even prevent a wasted trial. Since large multicentre trials are so expensive to conduct, even saving a single unnecessary trial would probably more than offset the cost of maintaining a national register of cancer trials.

Publication bias and meta-analysis

Many clinical trials are either undersized [8–10] or publish conflicting results; the results from such trials leave the questions of treatment advantages unresolved. This has led to the development of "overviews" or "meta-analyses", in which the results from a number of similar trials are pooled for analysis. One simple and naive way to perform a meta-analysis is to conduct a literature search and, for the trials so found, obtain details from the publications or by correspondence with the authors. However, many authors have demonstrated the existence of "publication bias" in which trials reporting statistically significant differences tend to be published more frequently than those failing to demonstrate a difference [11–14]. As a consequence, the reported improvement attributed to a new treatment may be an overestimate of the true treatment effect; in many cases the bias that occurs can be quite serious. These effects are of particular concern in meta-analyses, when an analysis based solely upon published trials located by a literature search may result in misleading conclusions [11]. This has led to agreement [11–14] that it is important to locate all relevant and suitable trials by using registers of trials rather than merely literature searches. In addition, since registers could contain information about the design of the trials, it would be possible to restrict further examination to trials which are identified as potentially well-conducted, such as randomised trials.

Disseminating information about results of trials

Since there are so many cancer-specific journals and general medical journals publishing reports of cancer clinical trials, it can be difficult for a practising clinician to keep abreast of the latest results relating to all the many disease sites. Registers allow clinicians to review the results and abstracts from publications relating to published trials, including trials only recently completed. This may assist in the selection of treatment for individual patients, possibly after obtaining supplementary details directly from the publications cited. In this context one might especially mention the PDQ data base (see below), which not only acts as a register of trials but also has a section providing "state of art" information on therapy.

Unnecessary duplication of clinical trials

Unnecessary duplication of trials should be avoided, not only because of the expense of conducting clinical trials, but also for ethical reasons [15, 16]. However, *unnecessary* is the crucial word [3, 17, 18], since replication of results can be important in confirming earlier reports and in demonstrating the general appplicability of treatments [19]; this is particularly true when the original trial is conducted within a single centre [20]. But the replication of trials should only happen intentionally and the planning should take account of the existence of similar trials; replication should not arise by accident, merely as a result of being oblivious to work carried out by other groups.

Registers provide a means of ensuring that those planning a new trial are able to check what other trials are in progress, and thus make an informed decision as to whether the proposed trial will contribute additional useful information [16]. Registers can also alert the funding bodies to the replication that is about to occur, permitting them to assess the benefits of it.

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Duplicate publication

Many medical journals have experienced duplicate publication of papers, in which authors fail to disclose that articles are being submitted simultaneously to several journals (self-plagiarism) or are divided up into numerous short reports (the least publishable unit, or salami publication) [21–23]. For example, a recent editorial on this topic was published simultaneously in seven leading paediatric journals [24–30]. Another recent paper [31] further suggested that duplicate publishing might be increasing, and reported that a Medline search showed that in 1990 12% of the main articles in the *British Journal of Industrial Medicine* had been published elsewhere. Apart from wasting time, for both editors and reviewers, valuable journal space is occupied to the exclusion of other papers which then have to be rejected or delayed. It may also serve to give undue weight to observations which are being reported several times over.

A few journals already run literature searches on authors whose papers they propose to publish [31], but this may fail to reveal that papers with different titles relate to the same trial, or that papers are being authored and submitted independently by different members of a team.

Registers, by linking abstracts to particular trials, make detection of these cases far easier for editors and referees. Also, when a duplicate publication has already inadvertently occurred, the entries in the register can make this fact clearer and ensure that the duplication is clearly identified.

It is sometimes claimed, mainly by authors seeking to gain a second publication, that duplicate publication may be of value in disseminating important results more widely. However, ease of retrieval from registers of trials, especially when abstracts of publications are stored, means that there is little rationale to this argument; it becomes simple for clinicians to browse through those entries that relate to their field of interest, and contrast the results of trials comparing particular treatments in specific disease areas. In any case, the editor should be given full information about the proposed second publication, so as to make the appropriate editorial decision. Thus, lest we ourselves be accused of the sin of plagiarism, the editor of the *European Journal of Cancer* was made fully aware of the similarity of some later paragraphs of this paper with those of a related, but more technical, paper specifically about the UKCCCR Register of Trials [1].

However, since papers may be submitted *simultaneously* to several journals, registers will only be able to play a major role in the elimination of duplicate publication if editors of journals are willing to notify the registries as soon as an article becomes accepted, so that the data base may be updated at the earliest possible time.

THE UKCCCR REGISTER OF U.K. CANCER TRIALS

Background

The UKCCCR was created to provide a forum for exchange of information and to recommend proposals for coordination of cancer policies within the U.K. An early task of the UKCCCR was to create a register of U.K. Cancer Clinical Trials, culminating in the 1986 U.K. Cancer Trials Register of the UKCCCR [33]. This consisted of a large book describing over 268 randomised and 80 non-randomised trials. However, this register was not implemented as a computerised database and no subsequent updates were made. Therefore, the UKCCCR funded the Medical Research Council (MRC) Cancer Trials Office at Cambridge to create and maintain a new register of all U.K. cancer clinical trials, in the form of an active on-line database [1].

Initially, current phase II and phase III randomised controlled clinical trials of cancer therapies will be included; later, closed and completed trials will also be collected, with abstracts of any published results.

It is intended to make the database as complete and comprehensive as possible, and to aim to include all trials conducted in the U.K. as well as international collaborative trials involving U.K. trials offices. In practice, it is likely that there may be difficulty in obtaining comprehensive registration of trials outside the public sector, since pharmaceutical companies may seek to preserve confidentiality in order to prevent competitors gaining advantages. However, it may prove possible to register such trials but withhold detailed information about them until they reach a certain stage, as agreed with the investigators [37].

Content

The content of the new UKCCCR database is largely based upon the 1986 register, but with some extra items. In addition, a workshop on Clinical Trial Registries in Brussels, Belgium, July 1991 [32], specified a core content of 23 items for registers, and recommended that all clinical trials registers should contain these items. The present register has been designed to comply with these proposals. It is also intended to store abstracts of any publications associated with the trials.

Summary analyses from completed trials will be stored when these are made available by investigators, including response rates, survival rates and related statistics [for example, treatment specific observed deaths (O_i), expected values (E_i), and the variance statistic (V)]; this should facilitate exploratory meta-analyses, although it may well still be necessary to obtain individual patient-based data in order to complete a more thorough analysis.

An example of the data being stored for a trial is given in Fig. 1. This shows the UK02 protocol which compares prophylactic cranial irradiation (PCI) vs. no PCI in small cell lung cancer of limited extent; this is an active multicentre trial, open to patient accrual, supported by the UKCCCR.

New trials will be added as they arise. The register will be updated regularly, and every 6 months a questionnaire will be sent out to investigators contributing studies. All of the major UK trials offices have connections to the UK academic network JANET, and so it is also planned to allow the coordinating centres interactively to update the records of their trials with information on patient accrual numbers, and status of the trial.

Access and availability

The initial data collection should be completed shortly, when it will be possible to use the prototype version of the browsing program to explore the database. In addition to the EuroCODE network, the register will be available for on-line browsing over JANET; JANET is also linked to other major international networks and thus the register will be widely available from many countries. Dial-up modem access will also be possible. Finally, it is intended to distribute subsets of the data, such as by organisation or by site, on PC diskettes; although the arrangements for doing this have yet to be finalised, it will have the advantage that users may print out neat copies on their local printers.

Because the software is expected to be used by other EuroCODE nodes, it has been written with portability, and the possibility of sharing it with others, in mind.

UKCCCR Reference No. : 000002

Trial No. : UK02

Title : UKCCCR/EORTC Prophylactic Cranial Irradiation Study (PCI)

Objectives : To compare, in a randomised trial, the effect of PCI in patients with limited disease SCLC and a complete response in terms of cranial relapse and survival. A supplementary aim is to monitor the patients' quality of life and cognitive function.

Randomisation Phone Number : 0223 322000 (for UK centres)
via EuroCODE for EORTC centres.

Collaborative Information : This trial is run in conjunction with the European Organisation for Research and Treatment of Cancer (EORTC). It is registered with the EORTC as trial no 08921.

Organising Body : United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR)

Funding Body : Medical Research Council (MRC)

TRIAL/TREATMENT DETAILS.

Trial Design : Multicentre, randomised.

Treatment Groups : 1. Immediate PCI treatment

2. No PCI treatment

Treatment Keywords : PROPHYLACTIC CRANIAL IRRADIATION, PCI, COGNITIVE FUNCTION, QUALITY OF LIFE, RADIOTHERAPY, SMALL CELL, SCLC, LUNG

PATIENT ELIGIBILITY AND TRIAL STATUS DETAILS.

Trial Status : Open

Patient Entry : New centres welcome

Country : Europe
Start Date : November 1991
Current Nos. : 42 **Target Nos.** : 200

Disease Definition.

Site : Lung **Histological Type** : Small Cell (SCLC)
Stage : Limited at presentation

Other Entry Criteria : Patient must show complete response to induction chemotherapy

ADMINISTRATION DETAILS.

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Data Centre : MRC Cancer Trials Office.
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Tel· 0223 311110.

Statisticians : David Machin
Based at data centre.

Data Manager : Richard Stephens
Based at data centre.

OTHER INFORMATION.

Miscellaneous Notes : Initially a 3-arm trial, launched in October 1987, (No PCI vs PCI with 36 Gy vs PCI with 24Gy) as a result of slow intake (100 patients in 4 years) it was relaunched in its current format in November 1991. The 100 patients accrued in the first version will be included in the final analysis.

Centres may opt to participate in either the basic comparison of survival and appearance of cranial metastases, or in addition the supplementary comparison of patients cognitive factors and quality of life.

Date entered : 5th October 1992

Date last updated : 5th October 1992

Fig. 1. Example of a printed copy of the entry for and active trial: the UKCCCR trial UK02, comparing PCI with no PCI in small cell lung cancer of limited extent.

OTHER REGISTERS OF CANCER TRIALS

EuroCODE and the European Register of Cancer Trials

Cancer trials are often collaborative or international, and so the European Community (EC) has been funding a project called EuroCODE [34, 35]. The aims of EuroCODE are to assist those concerned with cancer treatment to obtain the most up-to-date and reliable information available; to facilitate collaboration between the European Organization for Research and Treatment of Cancer (EORTC) and national groups to perform large trials or collaborative trials in rare tumours; to facilitate patient entry into clinical trials by providing interactive, computer-assisted patient registration and randomisation; and to enable rapid exchange of electronic mail between clinicians and investigators. The PDQ database can be accessed over EuroCODE.

Technically, EuroCODE consists of a network of computers, with national computer nodes based in the participating countries. Currently there are nodes in Belgium, France, Germany, Greece, Italy, The Netherlands and Spain; in the U.K. the UKCCCR-sponsored node is at the MRC Cancer Trials Office in Cambridge. It is planned to extend the network to incorporate other EC member states. 315 investigators from 17 European countries access EuroCODE on a regular basis.

The UKCCCR Register will be made available over EuroCODE, and any investigators with access to EuroCODE will be able to browse through the register of UK trials. The software is also being offered to the other EuroCODE nodes to support them in creating national databases of studies. Furthermore, the EC has agreed to fund a registry of European ongoing phase II and phase III trials as part of the European Action Against Cancer program, and will provide financial support for the collection of information about cancer trials conducted throughout the EC. This European database will become available in the course of the next few years, and will incorporate the UKCCCR register as a subset.

PDQ

PDQ is a database of cancer trials which is organised by the United States National Cancer Institute (NCI) [36]. PDQ contains information on over 1500 active trials, and already includes details of some European trials. However, entries in PDQ are both voluntary and selective. Trial organisations are encouraged to submit their protocols in a manner similar to submitting papers to a journal; the protocols are thoroughly refereed by the NCI sponsored PDQ board for scientific, medical and ethical soundness before being approved and accepted. Thus inclusion in PDQ serves as an endorsement for a trial. Full details from the approved protocols are stored on the PDQ database. Its major objective is "to help physicians identify trials appropriate for patients under their care, and so facilitate access to clinical trials" [5].

Relatively few European protocols are currently available through PDQ, and they are principally only those of the EORTC and a few national organisations conducting cancer clinical trials. However, the UKCCCR and other EuroCODE registers are intended to comprise a comprehensive database with respect to all European (EC) trials. Whereas PDQ provides detailed protocols on-line, these registers will store only brief summaries and abstracts; any clinician interested in participating in a trial would be expected to contact the appropriate trials office for a full protocol. Thus PDQ is a directory of approved trials, whilst these European databases are registers of all trials; they have different objectives from PDQ.

THE FUTURE OF REGISTERS

This paper has discussed the many reasons why registers of trials are so important. However, their value can only be fully realised when the registers are (a) complete and comprehensive within their defined field, and (b) have world-wide coverage. To ensure completeness of registrations of trials it has been suggested that both journals and funding bodies should make registration of trials compulsory [3, 37, 38]. Completeness is vital since, for example, anyone conducting a meta-analysis is likely to discover easily the large and well-known trials; but it is the inconclusive and often unpublished trials which may fail to be registered and by the same token fail to become included in meta-analyses. Geographical coverage is important because, for example, oncologists planning a large phase III trial in, say, renal cancer in the U.K. would be likely to know about most other relevant U.K. trials of importance; however, they may be less aware of all related trials in non-European countries, or even all those in other European countries.

The requirements of completenesss of entries combined with completeness of geographical coverage mean that individual national registers only partly fulfil the needs described above. International registers are vital. However, problems of arranging funding may result either in individual countries gathering their own data (like the U.K. register), or groups of countries collaborating (as the European register of cancer trials, incorporating the U.K. register as well as those of other European countries). As part of the collaboration standardisation of the data collected and the database structures makes combination of registers and cross-searching easier. In the longer term it may be hoped that a truly world-wide register of cancer trials may evolve.

CONTACTS AND INFORMATION

Please contact The UKCCCR Trials Register, MRC Cancer Trials Office, 5 Shaftesbury Road, Cambridge CB2 2BW, U.K. if you would like to be placed on the mailing list for future announcements about availability of the register, or if you know about other trials which you believe are not registered with us but ought to be.

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