Fate of research studies

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Summary

A retrospective survey was conducted of 720 research protocols, approved by the Central Oxford Research Ethics Committee between 1984 and 1987, to determine the fate of research studies from inception. Forty-five per cent were clinical trials, 23% were observational studies and 32% were laboratory-based experimental studies. Further information was obtained on 487 studies, of which 287 (59%) had been completed, 100 (21%) had never started, 58 (12%) had been abandoned or were in abeyance and 42 (9%) were still ongoing, as of May 1990. Forty-three per cent of the original 487 studies were subsequently published or presented. The most frequent reason for not starting a study was failure to obtain funding (40%). The main reason for abandoning a study was difficulty in recruiting study participants (28%). Departure of one of the investigators from the institution and a variety of logistical problems were also common reasons for either not starting or abandoning a study. A thorough review of the pragmatic as well as the scientific aspects of a planned research project is important to minimize the initiation of studies that are unlikely to succeed.

Introduction

A research project may falter at several stages in its progress from initiation to completion and ultimate publication. A study may fail to start or be abandoned prematurely, and, even if completed, the results may not be analysed or written up for a variety of reasons. There has been little discussion in the literature on the fate of research ventures. Research protocols approved by a research ethics committee offer an opportunity to examine the natural history of a cohort of research studies from inception. Although periodic surveys have been undertaken by several local and district based ethics committees in the United Kingdom, most of these have tended to focus more on committee practices and the ethical issues posed by the submitted protocols rather than on their subsequent outcome[1-6].

Information on the fate of research studies may be valuable for several reasons. Firstly, much can be learnt from other investigators about their experiences in research. Secondly, feedback to ethics committees about the fate of the protocols they review might help guide the future conduct of these committees and the advice they proffer to prospective investigators. Finally, there is a growing interest amongst government bodies and charitable funding agencies in the evaluation of research productivity and ways to minimize resource wastage[7,8].

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The main purpose of this study was to review the characteristics and fate of research protocols approved by a local research ethics committee and to determine those factors associated with their successful completion or otherwise. A secondary objective was to identify the magnitude of publication bias amongst the completed studies, and this is discussed in detail in another paper[9].

Methods

Study population and design

We conducted a retrospective survey of all research protocols submitted to the Central Oxford Research Ethics Committee (COREC) between 1 January 1984 and 31 December 1987. These dates were chosen on the basis of a pilot review of 75 studies, from which it was apparent that investigators had poor recall concerning information on studies initiated over 7 years ago, and that relatively few studies initiated after 1987 had been completed.

COREC was established in 1978, and is a joint committee of the District Health Authority and the Clinical Medicine Board of Oxford University. It covers the four main Oxford hospitals and three smaller associated hospitals, but also considers applications from general practitioners working in the district. The committee convenes once a month and currently reviews between 20 and 30 applications at each meeting. Since 1984, review of proposed research studies in psychiatry have been conducted by a separate ethics committee.

The titles of all protocols approved over the period 1984 to 1987, their COREC index number, and the name of the principal investigator were abstracted from a cardfile catalogue maintained by the committee. An introductory letter explaining the purpose of the study was sent to the principal investigator of each study, who was then contacted and interviewed by telephone for information on the current status of the study. If the study had never started or had been abandoned, we asked the reasons for this. For those studies that had started, we obtained further information on the design, organization, results and publication status. Co-investigators were contacted in the absence of, or at the request of, the principal investigator.

Questionnaires were mailed to 60 investigators (75 studies) who could not be contacted by telephone or who expressed a preference for a mailed questionnaire. The telephone interviews, coding, and verification of the completed questionnaires were conducted by one investigator (PJE).

For each study, information was collected on current status (ie completed, in progress, abandoned, in

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abeyance, or never started), the department in which the study was conducted, the number of data collection sites, use of a formal protocol, main purpose of the study, design (experimental or observational), main source of funding, prior sample size estimation and the method used, final sample size, number and type of comparison groups, data analysis (complete, interim or none) and the main study findings. For clinical trials, specific questions were asked about the treatment under evaluation, any comparison groups (concurrent or historical), randomization, blinding and the monitoring of adverse effects.

A taxonomy of study design terms was developed for use in data collection to ensure standardized coding of these terms. An *experimental study* was defined as one in which the investigator controlled one or more variables in order to monitor the effect on a process or outcome. Experimental studies were classified as either clinical trials or as 'other experimental studies' if the study was designed to learn more about the population under study, rather than about the procedure or treatment. Most of these studies were laboratory-based. An *observational study* was defined as one in which the investigator observed a process or disease without intending to alter it during observation.

Results

Approved research protocols

Between 1 January 1984 and 31 December 1987, 720 protocols, contributed by 372 investigators, were approved by COREC. One hundred and sixty-two (23%) were approved in 1984, 174 (24%) in 1985, 182 (25%) in 1986, and 202 (28%) in 1987. The median number of approved studies per investigator was 2 (range 1-17). Forty-five per cent were clinical trials, 23% observational studies, and 32% laboratory-based experimental studies. Almost two-thirds of the approved research protocols were contributed by 15 of the 40 departments that had submitted at least one protocol, reflecting the major academic interests of the hospital. These were (number of studies in parentheses): anaesthetics (73), diabetology (54), community medicine (45), obstetrics (40), nursing (34), general practice (33), respiratory medicine (31), dermatology (31), paediatrics/neonatology (31), cardiology (30), gastroenterology (25), orthopaedics (25), gynaecology (23) and ophthalmology (23). The median number of protocols approved per department was 13 (range 1-73). Thirteen research protocols were submitted from various non-clinical departments within the University of Oxford.

Thirteen of these 720 studies were subsequently withdrawn by the investigators because of ethical concerns, and five were excluded because they were intended for teaching purposes and not as research studies. One hundred and seventy-two studies (117 investigators) were considered lost to follow-up, either because the principal investigator had retired, died, or was currently resident overseas, or because there was no current or forwarding address and a suitable co-investigator could not be located. There were no refusals to the telephone interview and the response rate to the additional 75 mailed questionnaires was 63% (47/75). Inadequate information was provided by the investigators on 15 studies, and these were therefore excluded from subsequent analyses. Information was obtained on a total of 487 studies

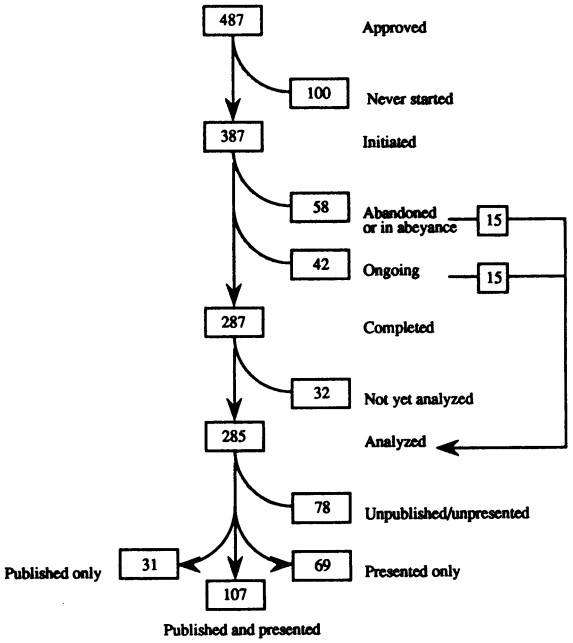

Figure 1. Natural history of 487 approved research protocols

contributed by 216 investigators. No significant differences were found between those studies for which the investigator was lost to follow-up or failed to respond to the mailed questionnaire, and those for which the investigator was located and interviewed, in the numbers of studies approved per investigator, year approved, the main department of study and the type of study design.

Status of 487 research protocols

Figure 1 provides a summary of the status of these 487 studies in May 1990. One hundred studies (21%) had never started, and 58 (12%) had been abandoned, of which 13 were reported to be only in abeyance. As of May 1990, 287 studies (59%) had been completed, either both enrolment and follow-up (54%) or enrolment alone (5%), and 42 studies (9%) were still ongoing. Of the completed studies, the median time from ethics committee approval to completion of recruitment and follow-up was 20 months with a range of 1-76 months. Two hundred and fifty-five of

Table 1. Reasons given by the investigator for a study never being started

Main reasons		
Failure to obtain funding	40	(40%)
Principal or co-investigator left institution	16	(16%)
Logistical problems*	11	(11%)
Anticipated difficulty in recruiting patients	10	(10%)
Adverse drug effects reported or drug withdrawn	8	(8%)
Loss of interest	7	(7%)
Too busy	6	(6%)
Technical problems†	2	(2%)
Total	100	(100%)

*Ward closures (3), publication of an identical study (1), limited drug supply (1), unable to administer intravenous drugs in an outpatient setting (1), flawed design (2), ward staff unwilling to cooperate with complex protocol (2), delayed approval from radiation protection board (1)

†Flawed assay or technique (1), existing laboratory equipment inadequate (1)

Table 2. Characteristics of initiated research studies

Study characteristic	*Study status*		
	*Total** (n=387)	*Completed* (n=287)	*Abandoned* (n=58)
Study design			
Observational study	110 (28%)	86 (30%)	13 (24%)
Experimental study	62 (16%)	51 (17%)	18 (31%)
Clinical trial	195 (50%)	148 (52%)	25 (43%)
Study groups			
Comparative	208 (73%)	209 (73%)	39 (67%)
Non-comparative	77 (27%)	76 (27%)	19 (33%)
Study protocol	298 (77%)	234 (82%)	38 (67%)
Thesis	75 (19%)	67 (24%)	8 (15%)
Pilot study	59 (15%)	48 (17%)	7 (12%)
No. of study sites			
Single centre	284 (73%)	216 (76%)	48 (83%)
Multicentre (2-5 sites)	64 (17%)	48 (17%)	6 (10%)
Multicentre (>5 sites)	39 (10%)	21 (7%)	4 (7%)
Main funding source			
Government	57 (15%)	37 (13%)	6 (10%)
Industry	144 (37%)	108 (38%)	13 (22%)
Private/Charity	42 (11%)	34 (12%)	2 (1%)
Department/Health Authority	67 (17%)	57 (20%)	11 (19%)
Unfunded	77 (20%)	49 (17%)	26 (45%)
Sample size			
<20	47 (17%)		
21-50	89 (31%)		
51-100	86 (30%)		
>100	39 (10%)		

*Includes completed, abandoned and ongoing (not presented separately on this table) studies, but excludes the 100 studies that never started

of the completed studies had been analysed, and 15 ongoing and 15 abandoned studies had also had an interim analysis conducted. At the time of the survey, 138 (48%) of the analysed studies had been published and 69 (24%) had been presented at meetings but remained unpublished.

Studies that never started

One hundred studies never started. There was no significant change over time in the percentage of approved studies failing to start. Minimal information was available on the design characteristics of these studies. However, compared to completed studies, there was no difference with respect to the principal type of study design. The main reasons given by the investigators for a study failing to start are listed in Table 1. The most common reason (40%) was a failure to obtain funding.

Initiated research studies

Table 2 summarizes the main characteristics of the 387 initiated research studies, for which further information was obtained. This excludes the 100 studies that never started. Approximately 257 studies (66%) were experimental in design, of which 195 (50%) were classified as clinical trials and 62 (16%) as laboratory-based experimental studies. The remaining 110 (28%) were observational studies, of which the majority were cross-sectional epidemiologic health surveys (51%), or laboratory-based studies (17%) involving the measurement of some biological parameter. Other observational studies were either case-control (12%) or cohort (27%) in design.

The majority (73%) of the research studies were single centre. Of the multicentre studies, Oxford was the co-ordinating centre in 40 (39%) and eight involved international collaboration. The main source of funding was from the pharmaceutical industry (37%). Of the 144 studies sponsored by the pharmaceutical industry, the protocol was written by the investigators in 60%, and by either the sponsors alone (20%) or by the sponsors in collaboration with the investigators (20%). Twenty per cent received no financial support. Thirty-two studies received funding from more than one source.

Patients served as study subjects in 87% of the projects. Twenty-three per cent involved hospital inpatients, 49% outpatients, with 3% from both sources and 12% from the community, usually through the local general practices. The remainder were either healthy volunteers (10%) or came from institutionalized settings (3%).

Table 3 summarizes the design characteristics of the 195 clinical trials and the 172 observational or laboratory-based experimental studies. Most of the clinical trials were either phase II (26%) or phase III (63%) with nine pharmacokinetic studies (phase I) and two phase IV trials. Ten could not be classified. Seventy-seven were designed to evaluate a drug, 13% a device or procedure (including radiotherapy) and 8% a policy or programme. Of these, only 44% were devoted to the evaluation of new as compared with established therapies. Only five of the studies involved the evaluation of surgical techniques. More than two-thirds of the trials employed a comparative arm, and of these, the comparison group received a placebo in 29%, other treatments or different doses/formulations in 46%, and no intervention in 13%. Randomization was the dominant method of treatment allocation (70%), and in all except six studies, treatment was assigned using formal randomization techniques, such as through central telephone

Table 3. Design characteristics of initiated research studies

Clinical trials (n=195)	
Comparison group	
Randomized	137 (70%)
Non-randomized	26 (13%)
Historical control	9 (5%)
No comparison group	23 (12%)
*Comparison treatment**	
Placebo-control	56 (33%)
Other treatments/formulations	90 (52%)
No intervention	26 (15%)
Blinding†	
Double-blinding	84 (56%)
Single blinding	35 (23%)
Unblinded	27 (18%)
Monitoring for adverse effects	154 (79%)
Experimental studies (n=62)	
Comparison group	
Concurrent	19 (31%)
Cross-over/own control	21 (34%)
Historical/external control	4 (6%)
No comparison group	18 (29%)
Observational studies (n=110)	
Comparison group	
Concurrent	44 (40%)
Cross-over/own control	2 (2%)
Historical/external control	7 (6%)
No comparison group	57 (52%)

*Excludes 23 studies with no comparison group
†Excludes 23 studies with no comparison group and 26 where comparison treatment was no intervention

randomization or sealed envelopes. The remaining studies used nonrandom or historical controls. In contrast, approximately half the observational or laboratory-based experimental studies either had no comparison group or used historical or external controls.

For completed projects, the median number of patients recruited was 100 (range 5-32 000) for observational studies, 26 (range 6-600) for laboratory-based experimental studies and 25 (range 6-5000) for clinical trials alone. Only 15% of all studies recruited more than 500 patients, and only 18% of trials involved more than 100 patients. In 58% of all studies and in 77% of clinical trials alone, there was a plan regarding the sample size before the study started, although this involved a formal sample size calculation in only just over half. For the remainder, the sample size was usually chosen on the grounds of expediency, such as the known availability of patients (36%), a time limit on funding (20%), estimates from previous studies (5%) or what was considered to be the usual number for the type of study performed (14%). Notably, only half of the studies with a planned sample size attained their target, and by far the most frequent reason cited for this was difficulty in recruiting study participants. Other less common reasons included a time limit on the study in seven, premature closure of a trial due to the emergence of either definite benefits in three or important adverse effects in five.

There was no significant change over time (1984-1987) in the number of studies that were comparative, in the number of trials that were randomized or in the composite score of the quality of trial design. There was also no statistically significant increase in the study sample size between 1984 and 1987, based on a linear regression line of sample size on year approved, which showed a slope not significantly different from zero.

Studies abandoned or in abeyance

Fifty-eight studies were abandoned or currently in abeyance. There was no significant change in the numbers abandoned each year over the period 1984 to 1987. Fifteen of these 58 abandoned studies (39%) were analysed, of which seven were subsequently published or presented. The median number of abandoned studies per department was two (range 1-9). Studies that were abandoned were compared to completed studies for differences in study characteristics (Table 1). Compared to completed studies, abandoned studies were more likely to be laboratory-based experimental studies (31% vs 17%), non-comparative (33% vs 27%), single centre (83% vs 76%), to lack a written protocol (67% vs 82%) and to be unfunded (45% vs 17%). There were too few abandoned clinical trials to reliably compare differences in the distribution of design characteristics with the completed trials. We estimated that a total of 906 patients participated in studies that were subsequently abandoned. The main reasons given by the investigators for abandoning a study are listed in Table 4. The most common reason (28%) was a difficulty recruiting study participants.

Discussion

The greatest attrition in the number of research studies occurred in the early stages of the research process, following ethics committee approval. Of the 487 studies for which information on current status was obtained, approximately one-third either never started or were subsequently abandoned. These findings are more or less in accord with two other surveys of ethics committee practices. A survey conducted by the Northwick Park research ethics committee found that about 40% of the projects approved over the period 1970-1978 had been completed, another 20% were still ongoing, and 20% had either been abandoned or never started[2]. A survey of the Southampton ethics committee in 1984, reported that the number of projects abandoned was only 3% in 1971, but that this had increased to 14% in 1975 and to 16% for the first part of 1979[5]. However, these surveys were all based on protocols approved in the 1970s, when the overall number

Table 4. Reasons given by the investigator for a study being abandoned or in abeyance

Difficulty in recruiting participants	16 (28%)
Technical problems*	9 (16%)
Principal or co-investigator left institution	8 (14%)
Logistical problems†	6 (10%)
Withdrawal of funding	6 (10%)
Null results	5 (9%)
Adverse effects	5 (9%)
Too busy	2 (3%)
Lost interest	1 (2%)
Total	58 (100%)

*Unreliable technique (8), specimens spoiled in transit (1)
†Appropriate equipment not available (2), associated study abandoned (1), difficulties with collaborators (2), closure of research unit (1)

of studies passing through ethics committees was much lower.

Failure to obtain funding was by far the most frequent reason for not starting a study, whilst the main reason cited for abandoning a study was that there were an insufficient number of study participants. It is noteworthy that many of the other reasons given for either failing to start or for abandoning a research study were similar. For example, a variety of logistical problems, such as ward closures or poor cooperation from nursing or laboratory staff, as well as the departure of one of the investigators prevented some studies from starting as well as halting their progress. This also draws attention to the problems that may arise from the increasing collaborative nature of research, particularly in the setting of a high turnover of junior staff. Other problems common to both failing to start or abandoning a study, were the emergence of reports of adverse drug effects from other studies, a loss of interest in the study or lack of time. The critical role that such non-specific issues may play in determining the viability of a study has been described previously[10,11]. Only five studies (9%) were discontinued by the investigator because of the finding of null results.

A decision not to start a study because of failure to obtain funding or in anticipation of other significant obstacles may in fact represent an appropriate 'screening-out' of poor quality research that might otherwise have foundered. It is the studies that were abandoned after initiation that are of more concern, since money, as well as the time and goodwill of patients and co-investigators will have been invested in a venture that has yielded minimal or no scientific return. We found that over a 4-year period, 906 patients were enrolled in studies that were subsequently aborted. The failure to analyse the data of completed studies has similar implications.

Most previous commentaries on the nature and quality of research have focused on published articles, usually in a specific discipline[12-14]. Our ability to comment on the adequacies of the research design of the studies in our survey is limited, since we examined only a few features of study design, and the appropriateness of the various designs and the sample size was not assessed in the context of the study question. However, some general comments can be made. Many of the research studies were single centre and based on a small sample size (approximately 50% of all studies examined had a sample size less than 50), and there was little evidence of improvement in this over time. However, in many cases, the small sample size was attributable to a failure to enrol sufficient patients, rather than to an absence of prior planning for an adequate number of patients. Although in general, studies of small sample size and low power should be discouraged[15], it is appreciated that small studies will remain a necessary preliminary step in the development and testing of new ideas, and may often be adequate in the controlled environment of laboratory-based experiments. The majority of clinical trials appeared to be of a satisfactory design, as determined by the frequent use of concurrent controls and random treatment allocation. In contrast, observational and laboratory-based experimental studies employed a comparison group in only 42% and 65% respectively. We were also interested in whether there were any consistently recognizable attributes of 'unsuccessful' studies (ie studies that never started or were abandoned). Minimal information was available on the characteristics of those studies that never started. However, we identified that abandoned studies were more likely to be single centre, unfunded (ie no external funding source), not to have a written protocol and to be non-comparative, compared with completed studies. These findings suggest that less time and resources were invested in the establishment of these studies. For these reasons, they were perhaps viewed as relatively dispensable when obstacles arose to their successful conduct.

One clear message from these findings for future investigators, is the importance of a thorough preliminary exploration of the pragmatic as well as the scientific aspects of a planned research project. Initiating research that is unlikely to succeed is unhelpful, wasteful of resources, as well as unethical. However, it is also evident that many problems cannot be anticipated and only come to light during the course of a study, hence the value of a preliminary pilot or feasibility study. Ethics committees have a particular responsibility to protect patients from studies that are unlikely to succeed and should adopt a more critical stance in their assessment of the scientific credibility and feasibility of proposed studies, including sample size. Investigators should be encouraged to seek statistical help more readily during the planning of their projects[15], and to challenge themselves with such questions as: 'Can this proposal/design adequately answer the question addressed?' and 'Is there an adequate patient population and sufficient means available for the study to go ahead?'.

Until recently, the supervisory role of ethics committees has been emphasized. There is now a move to encourage ethics committees to be more proactive not only in the evaluation of the scientific merits of proposed studies but also in monitoring their conduct once approved[16]. Such an audit of research activities within medical research institutions is likely to be well received by the funding bodies.

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Forthcoming events

International Conference on New Developments in the Pricing of Pharmaceuticals
20-21 February 1992, London
Further details from: Hilary Pendell, IBC Technical Services, Gilmoora House, 57-61 Mortimer Street, London W1N 7TD (Tel: 071 637 4383; Fax: 071 631 3214)

Colorectal Disease in 1992: An International Exchange of Medical and Surgical Concepts
20-22 February 1992, Fort Lauderdale, Florida
Further details from: The Cleveland Clinic Educational Foundation, 9500 Euclid Avenue, Room TT-31, Cleveland, OH 44195-5241, USA (Tel: 800 762 8173; Fax: 216 445 9406)

Impurities in Bulk Drug Substances
24-25 February 1992, London
Further details from: (see entry for 20-21 February 1992)

Application of the Principles of Good Laboratory Practice to Field Trials: Administration and Practice
5-6 March 1992, London
Further details from: (see entry for 20-21 February 1992)

Validation Therapy Conference: Breaking Through Dementia
10 March 1992, Queen Elizabeth II Conference Centre, London
Further details from: Angela Crowley, Age Concern England, 1268 London Road, London SW16 4ER (Tel: 081 679 8000; Fax: 081 679 6069)

Colposcopy
17-18 March 1992, RCOG, London
Further details from: Postgraduate Education Department, The Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG (Tel: 071-262 5425, ext 207)

Controlled Release Using Polymers: Characterization of Solid Drugs and Excipients
24-25 March 1992, Atlanta, GA, USA
Further details from: Pharmaceutical Division, Technomic Publishing Company, Inc, 851 New Holland Avenue, Box 3535, Lancaster, PA 17604, USA (Tel: 800 233 9936; Fax: 717 295 4538)

International Symposium on Recent Advances in Diagnostic Imaging and Radiation Oncology
24-27 March 1992, Kathmandu, Nepal
Further details from: Dr Naresh Prasad, Department of Radiology, Baylor College of Medicine, Houston, Texas 77030, USA (Tel: 713 798-4415; Fax 713 798-5556)

Update in Cardiopulmonary Pathology I - Cardiology
26-27 March 1992, National Heart & Lung Institute, London
Further details from: Postgraduate Education Centre, National Heart & Lung Institute, Dovehouse Street, London SW3 6LY (Tel: 071 351 8172; Fax: 071 376 3442)

Postgraduate Course in General Surgery
2-4 April 1992, San Francisco, California
Further details from: University of California, Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143 0742, USA (Tel: 415 476 4251)

Tinnitus and its Management
5-9 April 1992, Nottingham University
Further details from: Mrs J P Willoughby, Course Administrator, c/o Institute of Hearing Research, University of Nottingham, University Park, Nottingham NG7 2RD

Update in Cardiopulmonary Pathology II - Lung Tumours
6-7 April 1992, National Heart & Lung Institute, London
Further details from: Postgraduate Education Centre, National Heart & Lung Institute, Dovehouse Street, London SW3 6LY (Tel: 071 351 8172; Fax: 071 376 3442)

Mathematical Modeling of Pharmaceutical Data
7-8 April 1992, Atlanta, GA, USA
Further details from: (see entry for 24-25 March 1992)

Techniques & Applications of Molecular Biology: A Course for Medical Practitioners
7-10 April 1992, University of Warwick
Further details from: Dr Stephen Hicks, Department of Biological Sciences, University of Warwick, Coventry CV4 7AL (Tel: 0203 52340; Fax: 0203 523701)

Packaging of Healthcare Devices and Products
13-14 April 1992, Baltimore, USA
Further details from: (see entry for 24-25 March 1992)

3rd International Conference on SLE
13-15 April 1992, Queen Elizabeth II Conference Centre, London
Further details from: Dr Graham Hughes or Mrs Denzil Fletcher, Rheumatology Department, St Thomas's Hospital, London SE1 7EH (Tel and Fax: 071-633 9422)

Registration of Pharmaceuticals in Europe
20-21 April 1992, Nagoya
Further details from: (see entry for 20-21 February 1992)

British Association of Oral and Maxillofacial Surgeons: Spring Meeting
25-26 April 1992, Hospitality Inn, Glasgow
Further details from: Mr John Lowry, Honorary Secretary, British Association of Oral & Maxillofacial Surgeons, Royal College of Surgeons of England, 35/43 Lincoln's Inn Fields, London WC2A 3PN (Tel: 071 405 8074; Fax: 071 430 9997)

continued on p 79