International Society for Clinical Biostatistics News

Number 19 December 1995 Editor: David W. Warne

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Editorial

Welcome to the start of the 2nd decade of *ISCB News* ! When I started asking people for contributions to the News in the middle of November, I feared I would be lucky to produce an issue with 12 pages, but I'm delighted that so many people haven't minded me twisting their arms and have contributed interesting articles. And I also I hope you find some of them controversial enough to write about.

As is mentioned later in this issue, the ExCom will need several new members to serve from the Budapest conference. Please consider whether you would like to be a member and approach any of the ExCom for further information.

ISCB Constitution

Tony Johnson has done a magnificent job revising the ISCB constitution that you should all have received in October. Already several people have scrutinised the document and produced helpful comments. Please send all your comments to the ISCB Permanent Office, by the end of December, if possible.

Thanks once again to the contributors to this News: Marc Buyse, Bernhard Huitfeldt, Torsten Westermeier, Stephen Senn, Karsten Schmidt, Bela Hajtman, Jørgen Seldrup, Albert Cobos and Mike Campbell.

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ISCB Membership

Barcelona attracted 208 new members to ISCB, of whom 41 were former members: welcome to you all !

		Maastricht		Brussels		Cambridge		Basel		Barcelona	
		ISCB10		ISCB12		ISCB14		ISCB15		ISCB16	
		Sep89	end89	Jul91	end92	Sep93	Dec93	Jul94	Dec94	May95	Dec95
	Total	**276**	**261**	**859**	**596**	**377**	**715**	**305**	**698**	**425**	**725**
	# Countries	**19**	**23**	**30**	**32**	**27**	**32**	**22**	**31**	**30**	**33**
#	Country										
1	UK	33	50	86	90	128	176	51	120	98	144
2	France	29	30	78	52	26	62	21	50	46	73
3	Germany	39	30	80	67	39	75	42	84	23	71
4	Sweden	14	23	37	51	22	53	20	54	37	58
5	Spain		10	14	12	9	18	6	12	71	46
6	USA	13	18	227	45	16	40	14	39	25	41
7	Netherlands	94	14	46	30	23	38	22	33	23	36
8	Switzerland	10	14	24	25	8	22	68	80	14	33
9	Italy	11	16	47	33	23	37	8	32	13	32
10	Belgium	5	13	99	22	13	27	13	30	14	30
11	Denmark	3	4	14	58	23	38	8	31	16	30
12	Poland	1		3	11	2	11	4	24	2	24
13	Hungary		1	4	21	1	17	4	18	6	19
14	Norway	4	13	17	18	10	25	3	22	3	12
15	Austria	7	4	4	9	6	11	6	13	4	11
16	Canada	3	6	35	12	5	14	6	14	4	11
17	Australia	2	6	12	9	2	11		6	3	9
18	Finland	3	2	4	7	4	7	2	9	3	9
19	Japan	3	2	10	6	4	7	1	5	2	7
20	Israel		1	3	3	3	4	3	4	1	4
21	Hong Kong				1		1		2	2	3
22	Ireland	1	1	1	2	1	3		4	4	3
23	South Africa				1	3	4		1	1	3
24	South Korea									3	3
25	Brazil									2	2
26	Malaysia										2
27	Portugal		1	4	3	2	5		2		2
28	Slovenia			1	1	1	2	1	3	1	2
29	China				1	1	1		1		1
30	Czech. Rep.						1		1		1
31	India	1		1	1		1		1		1
32	Russia									1	1
33	Thailand			2	1		1			1	1
34	Cuba									1	
35	Iran									1	
36	Greece				1	1	1	1	1		
37	New Zealand				1			1	1		
38	Zimbabwe								1		
39	Kenya			2	1	1	1				
40	Turkey			1	1		1				
41	Columbia			1							
42	Mexico			1							
43	Philippines			1							
44	Kuwait		1								
45	Oman		1								

Aims of ISCB

The Society was founded to stimulate research on the principles and methodology used in the design and analysis of clinical research, to increase the relevance of statistical theory to the real world of clinical medicine, and to provide a common forum through meetings and publications for the exchange of knowledge, experience and ideas among clinicians, statisticians and members of related disciplines (e.g. epidemiologists, clinical chemists and clinical pharmacologists) working or interested in the field of clinical biostatistics.

Random Harvest

An Unending Muesli of Quotations Culled by Guernsey McPearson (Sixth helping !)

A strange form of cross-over trial ?

And I shall bide the first blow, as bare as I sit.
If there be one so wilful my words to assay,
Let him leap hither lightly, lay hold of this weapon;
I quitclaim it forever, keep is as his own,
And I shall stand him a stroke, steady on this floor,
So you grant me the guerdon to give him another,
sans blame.
In a twelvemonth and a day
He shall have of me the same;
Now be it seen straightaway
Who dares take up the game.

?, *Sir Gawaine and the Green Night*

N-of-1 trials ?

To see a world in a grain of sand

William Blake, *Songs of Innocence*

Sequential trials ?

'Where shall I begin please your Majesty ?' he asked. 'Begin at the beginning,' the King said, gravely, 'and go on till you come to the end: then stop.'

Lewis Caroll, *Alice in Wonderland*

Bioequivalence studies ?

Blood will have blood

Shakespeare, *Macbeth*

Pharmacokinetic pharmacodynamic modelling ?

What three things doth drink especially provoke ?

Shakespeare, *Macbeth*

Portfolio management.

My ventures are not in one bottom trusted,
Nor to one place; nor is my whole estate
Upon the fortune of this present year

Shakespeare, *The Merchant of Venice*

Computer Corner

In the next few months, I hope to have established a world-wide-web (WWW) homepage for ISCB, containing general information about the society and also about the forthcoming conferences in Budapest and Boston. Until then, have a look at the homepage of our hosts, IASC (International Association for Statistical Computing, like ISCB an affiliate of ISI, the International Statistical Institute):

http://www.stat.unipg.it/iasc/

Qualified and Experienced Statisticians

by Bernhard Huitfeldt

In the new CPMP biostatistical guidelines (December 1994), it is stated that an appropriately qualified and experienced statistician should be responsible for each clinical trial at all stages from design through to reporting. What is meant by this ? The European Federation for Statisticians in the Pharmaceutical Industry (EFSPI) has set up a working party, chaired by David Morgan of Marion Merrell Dow, which has the task of exploring the possibility of a common European definition of this concept. The intention is also to see if such a quality standard could be maintained through a system of certification of medical statisticians. In this working party, ISCB has been invited to participate with two delegates, Hans J Trampisch and myself.

The working party has met twice and has carried out some intermediate activities. It seems as if it should be possible to agree upon a definition of the quality standard based on a master's degree in statistics, including 1.5-2 years' courses in statistics and 3-5 years of professional experience in medical statistics. In addition, the requirement should include a documented ability to take full statistical responsibility of a medical investigation from design to reporting. These criteria are very close to those defined for a Chartered Statistician in the UK, even if that system does not incorporate the naming of different specialities. Also the German system for Zertifikat Biometrie in der Medizin has a similar perception of what should be meant by a qualified statistician. Representatives from Denmark, Holland, Spain, and Sweden have so far also declared a preliminary acceptance of these criteria.

The question of implementing a formal accreditation system for qualified statisticians is more controversial among the different countries. The idea of a pan-European system has been considered as unrealistic in the working party. However, based on a common understanding of what a qualified statistician is, we still believe that national systems for accreditation of medical statisticians are a possibility, where local considerations could be accounted for. If relevant co-ordination of such national systems could be satisfied, it would of course facilitate a mutual recognition in the future.

The definition of a quality standard for medical statisticians and the certification of our profession is a hot area. Many fundamental and practical arguments, pro and con, are easily mobilised. The working party welcomes any views on this issue and will continue to seek a broad consensus that could be accepted by a large majority of our members.

SEDREG Position Paper

SEDREG (Bernhard Huitfeldt, David Jones, Wolfgang Köpcke, Karsten Schmidt) is working on a position paper to be submitted to the *Drug Information Journal*. Comments are welcome. An outline is as follows: **(1) Background:** the increasing importance of statistics in clinical drug research; the development of statistics in the pharmaceutical industry; the use of statistical expertise in the European regulatory agencies (results of latest questionnaire); a comparison of Europe and USA; the 1991 RSS report; the formation of ISCB's SEDREG. **(2) Changes on the European scene:** new regulatory structures (EMEA, new member states and new procedures...); EFSPI, a new lobbying group; CPMP biostatistics guidelines; ICH guidelines; the statistics/clinical integration concept implemented; increased demand for efficient review. **(3) Implications for regulatory agencies:** statistical assessment of applications in addition to protocols; need for dialogue with industry on statistical issues; development of "regulatory statistics" as a discipline; in-house training of clinical assessors on statistics. **(4) More professional statisticians are needed in drug regulatory agencies:** a strong pressure from ISCB membership and EFSPI; strong and documented support from a wide range of national statistical associations; a necessary strengthening of the scientific competence of the agencies to complement other available specialists.

Stop Press !

Regarding the ICH guidelines "Note for guidance on Structure and content of clinical study reports" (ICH E3 Step 2 / Draft 13, 18 March 95, CPMP/137/95), and "Note for guidance on Good Clinical Practice" (ICH E6 Step 2 / Draft 9, 27 April 1995, CPMP/135/95), EFSPI made a considerable effort to review and comment upon the statistical parts of the documents. They were also successful in having these comments actually included in the version that the CPMP accepted as their suggestion for discussion at the Yokahama meeting in late November. John Shelton and Karsten Schmidt did a very good job to write up a consolidated review based on reviews from all the national associations.

The Role of ISCB in Promoting the Role of Biostatistics to Fight Scientific Fraud

or "A Plea for ISCB to DO Something !":
some personal views by Marc Buyse, ISCB President

At the end of last year, the President of the US National Academy of Sciences and the President of the US Institute of Medicine wrote:

> "*The responsibility for scientific conduct falls on all parts of the research community, including administrators, the leaders of scientific societies, and government officials.*"[1]

No member of ISCB who has heard of the case of fraud which has affected the NSABP (a large cooperative group conducting cancer trials) over the last few years can remain indifferent to their exhortation. The NSABP case was eloquently presented by Drs Ted Colton and Carol Redmond on the last day of ISCB16 in Barcelona. Those of you who are unfamiliar with the case may find detailed background information in the literature[2-5]. To recap the events briefly, an investigator in Montreal had falsified dates so that women with breast cancer would be considered eligible to enter a randomized trial carried out by the NSABP. The falsification was discovered by NSABP staff and duly reported to the National Cancer Institute (NSBAP's funding body). After months of an indescribable saga that resembled a soap opera more than a impartial investigation, Drs Bernard Fisher and Carol Redmond were removed from their respective positions of NSABP Chairman and Chief Statistician. The ruthless removal of these individuals whose personal integrity had never been questioned was felt by many to be a wholly inappropriate but "politically correct" decision aimed solely at appeasing the media and the public. The decision was taken in contravention to the most elementary requirements of a properly conducted investigation of alleged malpractice. These requirements were delineated earlier this year by the Presidents of the European Medical Research Councils:

> "*Staff who are the subject of allegations are entitled to expect that their work will be regarded as honest unless proved to be otherwise, and that they will be protected against ill-founded, frivolous, mischievous, or malicious complaints. ... The demands of justice also require that arbitration and appeal arrangements are available. Responsibility for establishing such a facility might be undertaken by national funding agencies and/or professional bodies.*"[6]

Here again, it is clear that professional societies such as ISCB are directly concerned. Should the ISCB get involved in the debate on scientific fraud ? My personal answer, which I hope will be shared by many of you, is an emphatic "Yes". Let me state some reasons why.

Biostatisticians should be involved in investigations of alleged fraud

What is infuriating in the NSABP case is that serious, irreversible and unjustified damage was inflicted upon a few dedicated individuals without any regard to the opinion of their peers. The statistical profession was largely ignored in the debate, and the public was either misinformed or seriously misguided on the substantive issues involved. The involvement of expert statisticians in the evaluation of this case might have resulted in a more balanced outcome, a fairer assessment of the responsibilities of those involved, and a more educated information of the public. Perhaps the most disturbing fact in the NSABP case is that the premise upon which it was based was fundamentally flawed. Once the word "fraud" was out, public outrage was inevitable, not only because patients with a serious illness were involved, but also because the "habit of truth" is the cardinal value in scientific endeavours. As Bronowski put it in *Science and human values*,

> "*The society of scientists is simple because it has a directing purpose: to explore the truth.*"[7]

Yet were the falsifications in Montreal aimed at distorting the truth ? Of course not. The investigator who committed the fraud had no intention of falsifying the trial results (as could have been predicted, the trial results were unaffected by the fraud). This in no way absolves this investigator from his fault, but it makes it plain that lynching expeditions were not called for.

Biostatisticians should be involved in designing ways of preventing fraud

In scientific fraud just as in medicine, "an ounce of prevention is worth a pound of cure". Fraud comes in many guises, including some that are innocent or even well-intended. In the NSABP fraud, the investigator cheated so that more of his patients could be randomized. His attitude, though scientifically and morally unacceptable, was perhaps not medically unsound if he genuinely believed that entry in this trial was in the best interest of his patients. The problem would not have occurred, had the inclusion criteria for the entry in the trial been less stringent, as most biostatisticians would like them to be. It is predictable that investigators will indulge in fraud if they feel that the clinical trials in which they are asked to participate are straight jackets that force them to do things that they would otherwise not do. Biostatisticians do have a major responsibility in deciding what is scientifically essential in a trial and what is not. Some of the more innocent cases of fraud could easily be avoided by making the trial part of clinical routine, rather than artificial experiments which bear little resemblance to it[8]. I was recently told of a general practitioner who filled in the quality of life questionnaires of his patients himself (he did not bother to disguise his handwriting and was thus easily caught). His excuse for cheating was that no one in their right mind would ever consider quality of life to be a relevant issue for the disease and treatment under consideration. This was certainly no excuse for falsifying the records, but he did have a point: on reflection, no one could figure out how a quality of life assessment ever got stuck into this trial !

Biostatisticians should be involved in designing ways of detecting fraud

For decades, engineers have made use of random sampling to control the quality of manufactured goods. It has always puzzled me that this simple concept, which is so central to industrial statistics, has been totally ignored in clinical research. For a "pivotal" clinical trial (that is, a trial which will be central to the application for approval), there seems to be an implicit dogma that all data reported to the statistical office need to be verified against the patient records. Such exhaustive verification results in monstrous monitoring budgets for such trials. It is not uncommon for monitoring to represent over 50% of a trial budget (to put things in perspective, the statistical activities usually represent a mere 5% of that same budget). It is absurd to spend so much time and money (especially in our days of universal budgetary constraints) on verifications that could be avoided. I doubt that medical knowledge is any better off as a result of the thousands of monitoring visits that are needed to ensure "100% case record verification". I also doubt that exhaustive verification is an efficient (let alone cost effective) way of detecting fraud. Statisticians know lots of tricks to detect strange data patterns that may point to the need of further investigation. As we all know, since R.A. Fisher's celebrated analyses of Mendel's data, even data that look all right may suggest cheating[(9)]. Inventive data manipulations are by no means recent: Charles Babbage (the far-seeing inventor of the calculating engine) established a catalog of such manipulations. Data "trimming", "cooking", and "forging" were already common place at the time his book *Reflections on the Decline of Science in England* came out ... in 1830[(10)] ! It is high time for the biostatistical profession to make a case for reasonable verifications of clinical data based on random sampling, and to suggest statistical methods for the detection of fraudulent or sloppy data. It is high time to recognize that "100% case record verification" is to GCP what bigotry is to religion: a caricature, not an essential feature.

Biostatisticians should be involved in estimating the likely impact of fraud

The likely impact of fraud on the outcome of an experiment also raises some interesting statistical questions. Returning to the NSABP case, was any bias introduced in the comparison of the randomized treatments because an investigator entered a few patients who, strictly speaking, did not meet the eligibility criteria ? Clearly not. As a matter of fact, the NSABP trials were re-analysed after excluding all data from the delinquent centre. Not surprisingly, the results of these re-analyses were almost identical to those initially published[(4)]. The fraud in Montreal was serious and inexcusable, but the response to it was, to say the least, out of proportion. It sets a precedent that may, if our profession remains silent, do more harm than good to future clinical trials.

> "*Because questionable research practices are generally not appropriate targets for government or legal investigations, the scientific community itself must take responsibility for determining which practices are serious enough to warrant institutional or professional responses and what forms these responses should take.*"[(1)]

The Role of ISCB in Promoting the Role of Biostatistics (part 4)

Why should ISCB get involved in all this ?

The NSABP affair has raised a lot of arguments and controversies, many of which highly political, and you might think that there is little point (or even, perhaps, some danger) for a society like ISCB to get involved in the debate. Let me disagree. Even leaving aside the unjustified harm that has been done to some of our colleagues, I believe that the NSABP affair has revealed that the statistical profession is insufficiently recognized as a partner in clinical research. If we, as professional biostatisticians, do not express concern in a case in which statistical principles have been ignored and the truth misrepresented, then we may indeed miss a chance to establish ourselves as partners in this field.

If, on the other hand, you feel concerned by these issues, please write. Whether you agree or disagree with the above ideas, your opinion counts. The future of our profession is at stake. As Alberts and Shine put it:

> "*If we do not police ourselves, others may step in to do so. The result could be a scientific enterprise that is increasingly constrained by legal strictures, financial oversight, and bureaucratic provisions. ... If scientific research is beset with paperwork and regulation, much of the joy and creativity in doing science could disappear. Such a cultural change would not only impede scientific progress, it would also make our field much less attractive to the dedicated and talented young researchers who represent the future.*"[(1)]

References

[(1)] Alberts B, Shine K. Scientists and the integrity of research. *Science* **266**:1660-1, 1994.

[(2)] Angell M, Kassirer JP. Setting the record straight in the breast cancer trials (Editorial). *N Engl J Med* **330**:1448-50, 1994.

[(3)] Fisher B, Redmond CK. Fraud in breast cancer trials (Letter). *N Engl J Med* **330**:1458-60, 1994.

[(4)] Fisher B, Anderson S, Redmond CK et al. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* **333**:1456-61, 1995.

[(5)] Christian MC, McCabe MS, Korn EL et al. The National Cancer Institute Audit of the National Surgical Adjuvant Breast and Bowel Project Protocol B-06. *N Engl J Med* **333**:1469-74, 1995.

[(6)] Evered D, Lazar P. Misconduct in medical research. *Lancet* **345**:1661-2, 1995.

[(7)] Bronowski J. *Science and Human Values.* Harper and Row, New York, 1965.

[(8)] Buyse M. Regulatory versus public health requirements in clinical trials. *Drug Inf J* **27**:977-84, 1993.

[(9)] Gigerenzer G, Swijtink Z, Porter T et al. *The Empire of Chance.* Cambridge University Press, Cambridge, 1989.

[(10)] Rao CR. *Statistics and Truth.* International Co-operative Publishing House, Burtonsville, 1989.

The Role of ISCB in Promoting the Role of Biostatistics (part 5)

CALL FOR SUGGESTIONS / CONTRIBUTIONS

If you are interested in contributing to a position paper on the role of statisticians in cases of scientific fraud, please drop me a note. All suggestions, comments and criticisms will be welcome. If (and only if) there is sufficient interest among the ISCB membership, I will set up a Working Party. If (and only if) a consensus seems to emerge on the need for a position paper, I will prepare a draft for discussion by the Working Party.

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1995 Conference Programme Chairman's Diary

by Mike Campbell, Southampton, England-UK

How do you get to be Chairman of the Scientific Committee of an ISCB Conference ? I am sure there are many ways, but in my case I believe it was because at ISCB14 in Cambridge in 1993 I had a room next to Eric Cobo. On learning he was from Spain, I tried out my O level Spanish on him. Mercifully I forgot all about the incident, but Eric was determined to get his revenge and about Easter 1994 send me a letter asking if I would Chair the Scientific Committee. When one is asked to do something there are always conflicting emotions, pleasure at being asked, doubt as to one's ability, belief that someone else (preferably Spanish) would be better and avarice at the thought of a trip to Barcelona. The latter won in the end and I accepted.

The first task of a Chairman is to assist in helping choose a committee. One has to balance statistical breadth with international coverage. We had to act quickly, because there was time for only one committee meeting, at the ISCB15 in July in Basel. Jørgen Seldrup, the Chairman of the Society, then visited Barcelona, to inspect the venue and finalise the committee arrangements. I then had a day trip to Basel for our one and only Committee meeting. It was at Basel that I met Mariano Sust, the secretary of the Committee, with whom over the coming months I was to exchange endless e-mails and Faxes, and from whom I was to learn something about the Catalans and their language. A small sub-committee, consisting of Peter Thall, John Whitehead, Albert Cobos (Chairman of the Local Organising Committee), Mariano and I met over lunch and discussed the next conference. One is faced with a tailor's dummy left from earlier conferences, the basic structure remains the same, but the choice of clothes is entirely up to you.

The main decision to be made was choice of plenary sessions and speakers, and one has the pick of the entire range of clinical biostatistics ! It is a wonderful opportunity to inflict one's own interests on others, at the risk, however, that no one will come to the conference. In the end we came up with: quality of life, design of trials, Bayesian methods, repeated measures, latent variables, Phase 1 trials and statistical refereeing.

(continued...)

This was too many and we decided to reduce it depending on availability of speakers. We also had to choose a topic for the Mini-symposium, and suggestions included head injury and management, prevention trials and antibiotic trials. Decisions had to be made quickly because we had to send out the First Announcement. We also had to choose topics for short courses.

I returned home after the trip to Basel with my head buzzing. I faxed Mariano so often before he obtained an email address that I knew his fax number by heart ! He was the chief worker and during the conference gestation he even managed to fit in becoming a father for the first time. We slowly added clothes to the dummy. A chance meeting with Max Parmer over coffee at another conference gave me the idea of Prevention Trials for the mini-symposium, and also its Chairman ! Dave Collett's reputation as an excellent lecturer was well known, and since he had just published a book on survival analysis, this seemed an ideal opportunity for a pre-conference course. Jim Lindsey was unknown to me personally at the time, but his book on repeated measures was well received and he had given a course at Leicester, so again we had another choice. We tried some other ideas as well such as data exploration and correspondence analysis amongst others, but these did not get off the ground. Statistical refereeing did not receive much favour amongst the committee so did not make the final programme, but we had invited Ted Colton onto the committee, who was keen to give a presentation, so we included an extended contributory session. Patrick Royston felt computer intensive methods would be popular, and so we dropped Phase 1 trials. We worked hard so that by Christmas we would have got all the speakers confirmed, so that when people applied to the conference they knew what they were getting !

The next key date was February 15th, which was the deadline for contributed papers. In the few weeks prior to the deadline we had only a few, but it is universal rule of conferences that everyone aims for the deadline, and so I was really pleased when we obtained about 160 contributions. We could only accommodate 96, so the committee had to grade each Abstract on a 1-5 scale. Each paper was seen by 2 members, and the total of the two taken. Mariano did a heroic job sending out the Abstracts and getting the scores from the committee members. It was my job to adjudicate major differences in score, decide on a cut-off score and arrange according to subject to fit into programme. In the end my office was too small to hold the array of paper, and I took over an empty office for an entire day to accomplish the task ! I allowed myself a small licence to fill empty slots with lower scorers and to omit some higher scorers who had topics not in line with the conference. Most potential speakers who were refused an oral presentation were offered a poster presentation. In order to encourage these (which can often be a better method of communication than oral presentations, especially for non-English speakers) I managed to persuade the Statisticians in The Pharmaceutical Industry (PSI) to donate a £50 book token.

After that, it was mainly up to the local committee, who did a wonderful job, particularly Albert Cobos. There are inevitable hitches; plenary speakers pulling out and last minute substitutions and session chairmen chairing sessions in which they were also speaking ! I was not convinced everything was going to be OK until the final session. As it happens, during the conference one of the plenary speakers was refused a visa, and it was only through urgent faxes from Mariano that they were allowed into the country in time for their talk !

However, in the end I think the conference went well; Barcelona is a beautiful city and the sun shone ! To sum up, chairing a scientific programme committee was a very worthwhile experience, and strengthened my links with many people and places. It made me appreciate how valuable and useful an organisation such as the International Society for Clinical Biostatistics is, and long may the Conferences continue !

President's Column

Dear Colleagues,

Those of us who had the good fortune to attend ISCB-16 in Barcelona will undoubtedly agree with me: it was simply the best ISCB meeting ever. Warmest thanks, again, to our Spanish and/or Catalan colleagues for their hospitality and dedication. I already look forward to another meeting in their country.

Arrangements for ISCB-17 in Budapest are progressing extremely well under the leadership of Professors Béla Hajtman (Local Organizing Committee) and Michael Schemper (Scientific Program Committee). There are not many pleasures associated with being President of a scientific society, but in my own case visiting Budapest to plan ISCB-17 certainly was one... I trust you have already marked your diaries for August 25-30 and have an Abstract in your word processor if not in the mail (deadline for submitting Abstracts: March 1, 1996).

The proposal for a new ISCB Constitution has been circulated and, judging from the incoming mail, reviewed carefully by many of you. Thanks to those who have sent in comments. I hope Tony Johnson will not give up before we have a final version to adopt in Budapest!

A last word of thanks to those who contribute to the Newsletter, the only link between ISCB members outside of the annual meetings. David Warne will accept (almost) any text at 100557.2260@compuserve.com.

With best wishes for a merry Christmas and a successful New Year.

Marc Buyse

The Polish Group of the ISCB

by Witold Kupsc, Warsaw, Poland

The Polish Group of ISCB was originated in 1990 by a group of 10 people, headed by Prof. Ewa Krusinska for the period 1990-93. Since September 1993, the elected representative has been Witold Kupsc. Membership has steadily increased over the years and the numbers attending the annual meeting, partially or fully supported by ISCB is as follows:

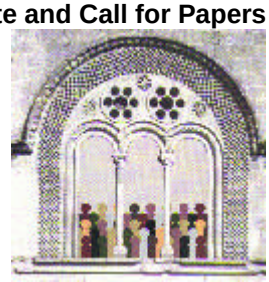
Year	1990	1991	1992	1993	1994	1995
Members	10	12	12	16	24	24
"" ""at ISCB	4	2	5	1	4	2

In June 1994, the seminar "Statistics in Clinical Practice" was organised in Warsaw by the Institute of Cybernetics of P&A Sciences, and the Centre of Postgraduate Medical Training with the cooperation of Polish Group members (Anna Bartkowiak, Wroclaw) for 100 participants. In October 1994, the Course of Biostatistics and Epidemiology in Warsaw was organised for 80 persons by the National Institute of Gentiology , Department of Epidemiology and University of North Carolina, Chapel Hill, Department of Biostatistics, with the collaboration of Witold Kupsc.

Since the start of the new academic year in September, there have been monthly meetings of members living near Warsaw (10 people). These have concerned discussing common statistical problems, and some invited lectures are being planned.

Announcement: Workshop on Statistical Modelling

First Announcement update and Call for Papers (deadline 15 January 1996)



11th International Workshop on Statistical Modelling
Orvieto, Italy: Monday 15 to Friday 19 July 1996

As in previous years this meeting will focus on the various aspects of statistical modelling, including theoretical developments, applications and computational methods. The workshop aims to concentrate on papers that are motivated by real practical problems and that make a novel contribution to the subject. Theoretical contributions addressing problems of practical importance or related to software developments are also welcome.

The scientific programme will include invited lectures and tutorials, contributed papers, posters and software demonstrations. Invited lectures will be presented by

A. Agresti	N. Best	A. Frigessi
H. Goldstein	T. Hastie	Y. Liang
D. Pregibon	N. Wermuth	

Contributed papers should be suitable for a 30 minute oral presentation (including discussion) and focus on motivation, statement of key results and conclusions, and emphasize examples with real data, wherever possible. A prize for the best presentation from a young statistician (details will be available later) will be awarded at the end of the workshop.

Papers and posters will be refereed and printed in a proceedings volume. Authors wishing to make a contribution to the workshop are invited to submit an abstract to A. Forcina, not later than January 15, 1996. Notification upon acceptance will be mailed by March 1st, 1996. The final manuscript, ready for reproduction, must reach the organizers by March 31, 1996. The workshop language is English.

When submitting a paper, please make sure that you meet the following guidelines: Abstracts need to include the title of the paper, name(s) of the author(s) and the full address for correspondence (including e-mail address, where applicable). To ensure proper evaluation abstracts should be approximately 3, but not more than 4 pages, and should give up to five keywords describing the content. Abstracts should describe the substantive problem and the data analysed, as well as the approach and models used. Also include a clear statement of the main results and conclusions and indicate the most important key references. Specify whether you wish to give an oral or poster presentation.

To prepare abstracts and manuscripts we encourage the use of TeX or LaTeX --- a template file abstract.tex is available either as the World Web page (URL http://www.stat.unipg.it/iasc/iwsm11.html) or by anonymous ftp from ftp.unipg.it in the directory /pub/stat/iwsm11. Submissions may be sent by e-mail to wks96@stat.unipg.it.

Scientific Programme Committee

A. Azzalini (Padova), J. Engel (Eindhoven), L. Fahrmeir (Munchen), A. de Falguerolles (Toulouse), A. Forcina (Perugia), B. J. Francis (Lancaster), R. Gilchrist (London), R. Hatzinger (Wien), P. van der Heijden (Utrecht), J. Hinde (Exeter), E. Lesaffre (Leuven), B. Marx (Baton Rouge), C. E. Minder (Bern), G. U. H. Seeber (Innsbruck), G. Tutz (Berlin).

Local Organising Committee

A. Forcina, A. Biggeri (Firenze), G. Galmacci (Perugia), A. Decarli (Milano), G. M. Marchetti (Sassari).

The participation fee, not including accommodation or meals, is Lit 270000, if registration and payment are made before May 15, 1996. The reduced full-time students' fee is Lit 100000. The late registration fee is Lit 350000. If you would like to submit an abstract or receive further information, please contact

Dipartimento di Scienze Statistiche, Universita' di Perugia,
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Letter to the Editor

from Cyrus R. Mehta, Massachusetts, USA

I am writing concerning the manner in which your June 1995 Newsletter refers to the EaSt software package developed by Cytel Software Corporation. I have noticed that this is the second issue of ISCB News in which you mention EaSt alongside a competing product, John Whitehead's Pest package, with an obvious bias in favor of the latter software. When referring to Pest you say:

"PEST3 is the new version of the highly successful sequential methods program produced by Reading University, England-UK, and used and supported by many leading pharmaceutical companies."

On the other hand, when referring to EaSt you say:

"EaSt, a commercially produced program for sequential designs has recently been offered to us by ISCB member Cyrus Mehta. The reviewer can keep the package for free afterwards !"

I find the contrast in your manner of describing these two packages rather insulting. I am at a loss to understand why it is relevant to state that the reviewer can keep the package for free afterwards. I'm sure that is a courtesy any software developer would extend to a reviewer who spend the time to provide an informative review. But from the way you have described our software, in two successive issues of ISCB News, one gets the impression that you are trying without much success to solicit a reviewer, with the added inducement that he can keep the package afterwards. We are not in need of a review of EaSt by ISCB, nor did we solicit it. We were asked by one of your officers if we care to submit our software for review and we agreed.

Our software package has a large customer base in the pharmaceutical industry, and is used regularly by the FDA because of its unique implementation of the Lan-DeMets alpha spending function methodology both at the design and the interim monitoring phases. One could just as easily your description of PEST and say "EaSt is a highly sequential methods program developed by statisticians at Harvard University, and Cytel Software Corporation, and is used and supported by many leading pharmaceutical companies".

We must now request you to either improve the tone of your description of EaSt, especially when contrasting it with PEST, or else return our software to us and cease to mention it at all.

So, here's the word from the reviewer:

Software Reviews: PEST & EaSt

Programs for Group Sequential Testing: EaSt (Version 2.0) & PEST (Version 3)

by Torsten Westermeier (Mainz, Germany)

The papers by Pocock (77) and O'Brien & Fleming (79) have popularised the group sequential approach, thus mitigating one of the major hindrances to the introduction of sequential procedures into clinical research, namely the predominance of fully sequential methods (which necessitate continuous monitoring) in the theoretical development of sequential analysis. They have constituted one branch of group sequential analysis that has its origins in the numerical methods introduced by Armitage et al. (69) for repeated significance testing. Most of the recent papers on group sequential analysis follow this approach. The other branch is based on advances in the theory of fully sequential procedures (Lai & Siegmund, 77) which have led to continuity corrections facilitating the use of group sequential testing. Whitehead made these methods available to applied clinical research in his well-known book 'The design and analysis of sequential clinical trials' (92).

(continued...)

Corresponding to these branches of group sequential analysis, two software packages are available: EaSt and PEST. Both are restricted to parallel group clinical trials. The former follows the repeated significance approach. The latter performs all calculations necessary for the application of the designs proposed by Whitehead (92). Due to their different approaches to group sequential analysis, the two packages are not interchangeable and therefore a direct comparison must remain limited.

Both packages have a menu driven interface and run on IBM-PC compatible microcomputers with MS-DOS operating system and EGA or VGA screen (PEST also CGA). A maths co-processor is not required but very useful to have. PEST uses about 2 MB of hard disk space, EaSt uses about 3 MB.

PEST follows the approach presented in the book of Whitehead (92). Although the methods are briefly presented in the user manual, I think it would be advisable to have access to the book as well. The procedures of PEST fall into four groups: 1. Design, 2. Simulation, 3. Monitoring, 4. Analysis. The design module includes 8 sequential designs (Triangular Test, SPRT, Truncated SPRT, Double Triangular Test, Double SPRT, Double Truncated SPRT, Restricted Procedure, Open Top Design) and the corresponding fixed sample design. These are available for 5 different response types (binary, survival, grouped survival, ordinal, normal) as well as for the general efficient score statistic. PEST outputs continuous boundaries in tabular and graphical form. Furthermore operating characteristic functions, expected sample sizes, median and 90th percentile sample sizes are calculated for different values of the unknown parameter. A new feature of the third version of PEST is the simulation module that allows one to simulate group sequential trials under various scenarios. In the monitoring module, trial results can be entered sequentially in grouped form. Here the continuity corrections to the continuous boundaries are computed according to the current interim analysis. A plot of the continuous boundaries with continuity correction and the test statistics observed so far is displayed. The analysis module outputs the p-value, median unbiased estimates, confidence intervals, the adjusted MLE with corresponding standard errors. Further functions are overrunning analysis and allowance for stratification and covariate adjustment (the latter needs SAS).

In contrast to PEST, the current version of EaSt is restricted to the design and monitoring of a group sequential trial, i.e. there is no possibility to get point or interval estimates after the trial has been stopped. At the design stage the user may choose between three types of response: normal, binary (using the normal approximation), survival. The next choice is between designs according to Wang & Tsiatis (87) which only allow the null hypothesis to be rejected and designs according to Pampallona, Tsiatis & Kim (93) which allow both hypotheses to be rejected. The shape of the boundaries in both designs depends on the parameter delta to be specified by the user choosing from a range from 0 to 0.5. These two extremes correspond to the O'Brien & Fleming and Pocock boundaries. For one- and two-sided tests of normal and binary responses EaSt computes maximum sample sizes and expected sample sizes under both hypotheses (also H1/2 for Pampallona-Tsiatis-Kim designs). If the response type is survival, EaSt outputs the estimated maximum duration of the trial, the maximum number of deaths, the accrual and expected study duration as well as the expected number of deaths under both hypotheses. For all design specifications the computed boundaries are given in tabular and graphical form. The calculations carried out by the design module of EaSt rely on the assumption of equal group sizes for the interim analyses. For unequal group sizes there is a further module that is misleadingly called 'the analysis module'. This module computes boundaries according to the alpha-spending approach of Lan & DeMets (83). The alpha-spending function is internally constructed by a linear interpolation of the cumulative error probabilities corresponding to 10 interim analyses with equal group sizes. After stopping the trial the actual power of this test is calculated.

(continued...)

The advantage of PEST is its comprehensive treatment of all parts of a clinical trial. I hope that future versions of EaSt will also contain some of the known procedures for analysis of the results of group sequential trials. However, my impression is that the interface of EaSt is more user-friendly. For example, in PEST there is no possibility to save text and graphical output to a file or printer. Instead, PEST assumes the user to have a facility to obtain hard copies of the screen images produced by PEST. Furthermore the comparison of varying design specifications is easier in EaSt (where different plans are summarized in one 'study') than in PEST where the user is always forced to start with the first of the interactive menus. Due to the underlying theory the calculations carried out by PEST (except the simulations) do not need more than a few seconds (on a Pentium processor, 75 MHz, 16 RAM). The computing time needed by EaSt depends on the number of interim analyses, for example the calculation for 5 interim analyses took about 15 seconds (10 interim analyses, about 35 seconds). If standard designs are chosen, EaSt takes the results out of an internal look-up table. In my view one disadvantage of EaSt is that the design specifications are restricted to Wang-Tsiatis and Pampallona-Tsiatis-Kim designs. Although these designs cover most of the practically relevant designs I would like to define boundaries of my own choice.

For my personal use I see no alternative to the PEST package whereas for the repeated significance approach I prefer one of the FORTRAN programs usually distributed by the authors of papers on group sequential testing (e.g. Reboussin et al., 92). Although this FORTRAN program is not as user friendly as EaSt it offers more features (e.g. confidence intervals) and the opportunity to change the source code to my own needs. However, these programs are of course no alternative to those statisticians who need to use validated commercial software packages.

References:

Armitage, McPherson & Rowe (1969): Repeated significance tests on accumulating data. JRSS A, 132, 235-44.

Lai & Siegmund (1977): A nonlinear renewal theory with applications to sequential analysis. Ann. Statist., 1, 946-54.

Lan & DeMets (1983): Discrete sequential boundaries for clinical trials. Biometrika, 70, 659-63.

O'Brien & Fleming (1979): A multiple testing procedure for clinical trials. Biometrics, 35, 549-56.

Pampallona, Tsiatis & Kim (1993): Spending functions for the type I and type II error probabilities of group sequential tests (under revision for Biometrics).

Pocock (1977): Group sequential methods in the design and analysis of clinical trials. Biometrika, 64, 191-199.

Reboussin, DeMets, Kim & Lan (1992): Programs for computing group sequential boundaries using the Lan-DeMets method, Technical Report 60, Department of Biostatistics, University of Wisconsin-Madison.

Wang & Tsiatis (1987): Approximately optimal one-parameter boundaries for group sequential trials. Biometrics, 43, 193-99.

Whitehead (1992): The design and analysis of sequential clinical trials. 2nd ed., Ellis Horwood, Chichester.

1995 AGM Minutes

from Stephen Senn

Site: ISCB16, Faculty of Biology, Barcelona, Wednesday 2 August 1995, 14:00

Present: 53 members.

1 Secretary's Report.

The secretary reported that it had been a very quiet year. The most important development had been the contact made by Professor Helmut Schaeffer with EC on behalf of the guidelines subgroup of ISCB. This subgroup consisted of the Vice-President, Karsten Schmidt, the Secretary and Professor Schaeffer. A verbal assurance* had been received that ISCB would be put on the circulation list for EC guidelines affecting drug-regulation. Professor Schaeffer addressed the meeting inviting those members who wished to receive copies of guidelines to write to him expressing their wish to do so but expressed the hope that only persons who were seriously interested in commenting through the Society would do so as the administrative load for him and his secretary would be considerable.
(*NB During the course of ISCB16 but subsequent to the AGM, Professor Schaeffer received written confirmation of this offer.)

2 Treasurer's Report

2.1 The Treasurer presented the accounts. The economic health of the Society appears sound.
2.2 The membership fee would be maintained at £15.
2.3 There were proposals from the floor that various schemes of support for attendance at ISCB meetings, including reduced registration for students and grants for persons from countries with currency restrictions might be funded by the Society. The meeting was informed that this was a matter that would be considered by the executive committee.

3 President's Report

3.1 The President drew attention to the progress in drafting a new constitution. He thanked Tony Johnson for the considerable efforts he had made in drafting this.
3.2 He also thanked the Newsletter Editor for his work in once again producing two issues between two AGMs. He appealed to members of the Society to maintain and improve the quality of the Newsletter by contributing pieces especially book and software reviews.
3.3 He mentioned that the ExCom would be investigating the possibility of having a home page on the world wide web.
3.4 The President drew attention to the position paper for SEDREG being prepared by the Vice-President and Treasurer and which would be submitted to the *Drug Information Journal* by the end of the year.
3.5 He called upon members of the society who were prepared to organise future meetings of the Society to make themselves and their proposals known to the ExCom.

(continued...)

Minutes of the Annual General Meeting 1995 (continued)

4 Constitution

4.1 Tony Johnson gave a brief history of the constitution pointing out that the Society had survived without one until 1982 and had revised it at roughly two year intervals since.

4.2 Drafts of a new constitution had been prepared by him and circulated amongst ExCom members. A version approved by the ExCom would be sent out to the members in September 1995 for wider comment. At least 90 days before the Budapest meeting members would receive a final draft, together with a substantive motion moving adoption and a proposal for the interim period until a new constitution could come into effect. This would then be voted on at the AGM at ISCB17 in Budapest in August 1996.

5 Voting for Membership of The ExCom

5.1 There were three nominations (Albert Cobos, Nancy Geller, Irene Guggenmoos-Holzmann) for two vacancies. A vote was held under the supervision of nomination committee members, Roel van Stik and Maria Valsecchi as a result of which Albert Cobos and Nancy Geller were returned.

5.2 The President thanked Irene Guggenmoos-Holzmann for her contribution to the ExCom over the last two years and congratulated Albert Cobos on his appointment and Nancy Geller on her re-appointment.

6 Appointment of Auditors

6.1 Suzanne Moeller has offered to continue as auditor for the Society's accounts. This offer was gratefully accepted.

6.2 Albert Cobos informed the meeting that José-Maria Sol has agreed to audit the accounts of ISCB16. This offer was gratefully accepted.

7 Appointment of Member of the Nomination Committee

The secretary informed the meeting that the departure of Roel van Strik would leave a vacancy. No volunteers being forthcoming, Doug Altman graciously accepted the Secretary's request to fill this office.

8 SEDREG

8.1 The Vice President, Karsten Schmidt presented apologies from W Koepcke for absence.

8.2 Karsten drew attention to the article in the June issue of *Applied Clinical Trials* by Peter O'Donnell describing the position of statistics in drug regulation in Europe.

8.3 He confirmed that a position paper would be finalised in the autumn.

9. Future Meetings of ISCB

9.1 Bela Hajtman presented two short videos about ISCB17: one on the conference site and one on Budapest itself. These were welcomed with enthusiasm and applause by the members.

9.2 Nancy Geller gave an outline of the plans for the joint meeting with the Society for Clinical Trials in Boston in 1997. Ted Colton also reported on this,

10 Matters Arising from ISCB15

(This matter had been held over from the beginning of the meeting because the minutes had not yet been photocopied.) G Nehmiz reported that he had audited the accounts and that these were in order.

11 Close of Meeting

The President closed the meeting at 15:45 and called on members to meet again in Budapest.

Multi-Centre Trials and the Finally Decisive Argument

by Guernsey McPearson

In my career as a medical statistician in drug development, I never found anything quite as effective in winning disputes as the Finally Decisive Argument. For the benefit of readers of this journal, I illustrate its force with the example of that old chestnut, not to say canard or red-herring (food for thought ? appropriate for menu-driven drug development programmes ?): type II and type III sums of squares.

The following is a Socratic dialogue between two statisticians, one of whom is of the McPearson school of statistics and one who is not.

Secundus: I see, Tertius, that you have weighted all centres equally in your estimate of the treatment effect. Why is that ?

Tertius: It is because, Secundus, any other weighting would be entirely *arbitrary*.

Secundus: This does indeed appear to be an excellent reason Tertius. However, I am puzzled to understand one thing, and that is on what basis you chose the centres in your trial ?

Tertius: Oh that is quite simple, Secundus. All the physicians concerned have good reputations and promised to deliver an adequate number of patients.

Secundus: These are indeed excellent reasons, oh Tertius. However, I cannot help noting that, although some physicians have indeed provided many patients, some seemed to have delivered very few patients at all.

Tertius: Indeed, some of the physicians have disappointed me, but when running trials in future I will not use them.

Secundus: A very wise precaution, Tertius, but it seems to imply that provided centres perform well, you do not mind which centres are in the trial.

Tertius: This is indeed true Secundus, the main thing is to have enough high quality data.

Secundus: I see. So that provided only that the centres delivered enough patients in total you would be indifferent as to whether the trial was based on, say, centres 1,3 and 7, or on centres 4, 5 and 8, or on centres 1,2, 8 and 9 or indeed on any set of centres.

Tertius: That is indeed so, Secundus.

Secundus: And suppose, for argument's sake, that centre 3 could give you all the patients you needed would you use it alone ?

Tertius: (Smiling) Indeed I would Secundus. This would make life much simpler. Unfortunately, clinical trials don't usually work like that.

Secundus. What a pity. And if centre 4 could give you all the patients you needed would you be happy to use that ?

Tertius: Of course, Secundus. The centre is unimportant.

Secundus: But this implies Tertius that you are quite happy to base your treatment estimate on centre 3 alone, if only it has enough patients and on centre 4 alone, if only it has enough patients and indeed on any centre at all, provided it has enough patients.

Tertius: (Impatiently.) Quite so. This is obvious.

Secundus: But then, your only preference amongst centres is based on the precision of the information which they provide, not on any peculiar feature of any given centre and, since you are otherwise indifferent between them, I fail to understand why you insist on weighting them equally and in an inefficient manner.

Tertius: I begin to understand your point, but what is the alternative ?

Secundus: The alternative is to weight the centres in such a way that the precision of the treatment estimate is as high as possible.

Tertius: But does that not correspond to the Type II philosophy ?

Secundus: It does indeed.

Tertius: Then I am sorry, Secundus, but you have been wasting my time. That is a dangerous heresy.

Secundus: Why so ?

Tertius: Because the Finally Decisive Argument says so.

Secundus: In that case I do indeed apologise for having wasted your time, Tertius. The Finally Decisive Argument is transcendental in nature and cannot be defeated by mere logic.

Next issue. The Finally Decisive Argument is used to prove that drug development is just like skiing. If you want to succeed, you must stick to parallels and avoid the cross-overs.

Letter Home From Barcelona

from Jørgen Seldrup

You must have wondered, what had happened to me, since you had not heard from me for a very long time. Well, a lot has happened to me, but I will tell you about that another time. Right now I want to tell you about my visit to Barcelona. This is a lovely place, warm and sunny and populated with friendly people, I think; communication with the locals is not what it could be, as they seem not to know any Danish and my Spanish is non- existent. Still we have all got arms and legs and ...

We landed at Barcelona airport at lunchtime on Saturday to take advantage of the travel industry's perfectly logical requirement that if you would like to spend the weekend in a nice place, then you should be rewarded with a cheap ticket. By the way, naming the airport "The Prat" makes you wonder what you have let yourself in for.

Well, having arrived safely at The Prat the next stop was the hotel '...within walking distance of the conference venue'. We got there after having used arms and legs and... But I have often wondered, when seeing notices on billboards like, four minutes to so and so, turn left at the third traffic light, go through the next two roundabouts, turn right at the first T-junction and abracadabra, you are there. I suppose everywhere is within walking distance - and so it turned out with my hotel.

I had a splendid weekend before the conference, when we went with some Spanish colleagues along the coast to Costa Brava. Now, I have never been there before and I have never had such an introduction to 'a new place' before. Having driven to a small local airport (which might more aptly have been called The Prat) we boarded a little fourseater and flew over the cuckoo's nest; strange to be in a plane where you can open the windows and where the air-conditioning is a plastic tube sticking out of the side where the wing is attached - still, it was easy to regulate for the pilot though.

What else ? Oh yes, the reception on the first day of the conference was interesting. We all went to this royal palace across the road set in a peaceful park. The weather, need I say, was beautiful. I got there a little late, but that turned out not to matter, as the city dignitary had had some problem arriving through the traffic. But a good time was had by everybody, drinking and eating and generally lazing about on the grass until somebody noticed some small sign saying 'don't tread on the grass'.

About the conference itself. Let me assure you that it was good, really good, but I will not bore you with any details of the presentations, but there was the usual mix of overheads upside down, slides crammed full of mathematical formulae, the elusive lost slide, the interruption of the local power supply; but nobody dropped their entire presentation on the floor and the majority mastered the art of pointing to relevant parts of their slide with variously shaking fingers, moving pencils and the wandering infrared pointer; the dress code, as you can imagine, was not exactly adopted from 'the Lord Mayor's Ball', but it was nice with a bit of air round your knees. My price for the best quote of the conference went to the speaker, who was discussing various aspects of quality of life when he proclaimed that "Quality of life is seriously reduced after death".

Right, I am running out of space now so take care until I see you again - if not before, then in Budapest next year.

JS

1994 Conference: Au Revoir II

ISCB 15 - Bâle Basel Basilea Basle 94

from auditor Gerhard Nehmiz, Biberach-an-der-Riss, Germany

The account of the 15th ISCB congress was reviewed in Basel on 11/04/1995. The following criteria were investigated: (1) completeness of the records, (2) correctness of the calculations, (3) adequateness of the expenses in relation to the aims of the ISCB. Criteria (1) and (2) could be investigated by sample only, which did, however, cover the areas of highest weight. Criterion (3) was kept in mind throughout.

The special account has meanwhile been closed, and the remaining balance has been transferred to the general ISCB account. I received confirmation of this on 17/08/1995. The summary report of Mr. Schenker and Mrs. Rieser is enclosed.

In every respect, the result of the overview was completely satisfactory. I recommend approval of the accounts. I thank Mr. Schenker and Mrs. Rieser for their help.

Account (CHF)	CHF	CHF
Income		
Conference fees	166,889.70	
Exhibition and advertisements	16,991.10	
Sponsors	23,005.50	
Bank interest	278.85	
Various income	11.50	
Courses	17,500.00	
Advance ISCB	11,100.00	
TOTAL	235,776.65	
Expenditure		
Conference rooms		26,960.00
Technical equipment		4,868.30
Conference extras		13,114.85
Social programme		55,017.70
Convention services		43,040.00
Stationery		13,552.00
Invited speakers		25,956.45
Guests		1,580.00
Refunds of fees		5,146.60
Banking fees and taxes		409.55
Courses		6,012.00
Audit		198.75
Repayment advance ISCB		9,230.00
Bank transfer to ISCB		30,690.45
TOTAL		235,776.65

ISCB Advertising Rates

The current costs are:

Full A4 page: £180
Half A4 page: £100
Quarter A4 page: £ 60

Additionally, we will include loose flyers with the distribution of the newsletter at an initial handling cost of £25. However, if the addition of the flyer(s) increases the postal charges, the advertiser will also be charged the difference in distribution costs. For further information, please contact the editor.

Books and Software for Review

Books

(1) The following books are available for review. Please contact the editor if you would like one or more of them. Reviewers are allowed to keep the book(s) that they reviewed (3.5" disks or email preferred, deadline for reviews: end of March 1996). Publishers: I would be very grateful if you would send some new books !

Marcel Dekker, New York & Basel:

Carstensen JT (1995)
Drug stability - Principles and practices. 2nd edition

Harris EK & Boyd JC (1995)
Statistical bases of reference values in laboratory medicine

Kocherlakota S & Kocherlakota C (1992)
Bivariate discrete distributions

Lutz EW (ed) (1991)
Future demographic trends in Europe and North America: What can we assume today ?

Welling PG & Tse FLS (eds.) (1995)
Pharmacokinetics: regulatory, industrial, academic perspectives. 2nd edition.

PWS-Kent, Boston:

Scheaffer RL (1990)
Introduction to probability and its applications

(2) Reviews awaited:
Juia Singer: Maxwell & Delaney (Wadsworth): Designing experiments and analyzing data: A model comparison perspective
Ott & Mendenhall (PWS-Kent): Understanding Statistics

(3) Reviews still awaited:
David Owens: Guarino (Marcel Dekker): New drug approval process
Singer & Upton (Marcel Dekker): Guidelines for laboratory quality auditing
(If anyone knows this person, please ask them to pass on the software to someone who will review it !)

Software

(4) Reviews still awaited:
Stephan Evans: N, Nsurv, TESTIMATE (IDV, Gauting)
Joan Houghton: Random (Wiedey) and Rancode (IDV)
(If anyone knows these people, please ask them to pass on the software to someone who will review it !)

ISCB 17 - Budapest 96

ISCB-17 in Budapest, Hungary

from Bela Hajtman

Scientific Programme Committee

Chairman Michael Schemper (Austria)

Committee Members

Per Kragh Andersen (Denmark)
Lutz Edler (Germany)
Els Goetghebeur (The Netherlands)
Anthony Johnson (United Kingdom)
Alessandro Liberati (Italy)
Ettore Marubini (Italy)
Stephen Senn (United Kingdom)
Richard Simon (USA)
Gábor Tusnády (Hungary)
Janet Wittes (USA)

Local Organising Committee

Chairman Béla Hajtman

Committee Members Artúr Hoffmann, Péter Vargha, József Vitrai

SCIENTIFIC PROGRAMME

Plenary sessions

Topic i: Philosophy, Past and Future of Clinical Biostatistics

David R. Cox (Oxford University, UK): The Relation between Theory and Application in Medical Studies

Edmund A. Gehan (Georgetown University, Washington, USA): Lessons from the History of Biostatistics

Hans van Houwelingen (Leiden University, The Netherlands): The Future of Biostatistics: Expecting the Unexpected

Topic ii: Graphical Methods in Clinical Research

Rex Galbraith (University College London, UK): Application of Radial Plots in Clinical Biostatistics

William S. Cleveland (AT&T Bell Labs, Murray Hill, USA): Trellis Display of Data from Designed Experiments

Leland Wilkinson (SPSS, Evanston, USA): Graphical Displays for Aggregate and Disaggregate Data

Topic iii: Explained Variation in Statistical Models

Richard Simon (National Cancer Institute, Bethesda, USA): Distinctions among Explained Residual Variation, Explained Risk and Goodness of Fit

Michael Schemper (Vienna University, Austria): Explained Variation for Logistic Regression

Janez Stare (Ljubljana University, Slovenia): Explained Variation for Cox Regression

(continued...)

Topic iv: Disease Clustering and Geographical Analysis

Geoffrey M. Jacquez (BioMedware, Inc., Ann Arbor, USA): Disease Cluster Tests for Uncertain Locations

Andrew Lawson (Abertay Dundee University, UK): MCMC Methods for Clustering with Case Event and Count Data

Sylvia Richardson (INSERM, Villejuif, France): Ecological Analyses: Methods, Design, and Interpretation

Topic v: Statistical Methods in Genetics

Max Baur (Bonn University, Germany): Association Studies with Internal Controls in Genetic Epidemiology

Françoise Clerget-Darpeux (INSERM, Paris, France): Use of Genetic Markers for the Study of Multifactorial Diseases

Endre Czeizel (National Institute of Hygiene, Budapest, Hungary): Analysis of Clusters in Medical Genetics

Mini-Symposium: Health Care Assessment and Pharmaco-Economics
Chairman: Alessandro Liberati (Mario Negri Institute, Milano, Italy)

Contributors:

John Urquhart (Rijks University Limburg, Maastricht, The Netherlands): Pharmaco-Economic Evaluation: Terms of Reference

Hamiran Gafni (McMaster University, Hamilton, Canada): Pharmaco-Economics: An Health Economist's Perspective

Frank Harrell (Duke University, Durham, USA): Economic Evaluation in Observational Studies

Sheila Gore (MRC, Cambridge, UK): Economic Evaluation in Clinical Trials

Franco Sassi (London School of Economics and Political Science, UK): The Use of Economic Data in Systematic Reviews

Mihály Kökény (Ministry of Health, Budapest, Hungary): Economic Evaluation of Health Care Interventions in Hungary

Courses (full day, 4x90 minutes):
Pre-Conference Courses (Sunday, 25th August)
A: Principles and Methods in Survival Analysis
Lecturer: Maria G. Valsecchi (Milan University, Italy)
B: Extending the Cox Model
Lecturer: Terry Therneau (Mayo Clinic, Rochester, USA)
Post-Conference Course (Friday, 30th August)
C: Statistical Methods for Genetic Epidemiology
Lecturers: Robert C. Elston (Case Western Reserve University, Cleveland, USA) and Daniel Schaid (Mayo Clinic, Rochester, USA)

Further Information
Call for Registration will be mailed in February 1996. Enquiries before then should be addressed to:

ISCB–17 Secretariat
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H–1371 Budapest 5
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Semmelweis University of Medicine — a Short History

from Béla Hajtman

The host of ISCB–17, Semmelweis University of Medicine stands out as one of the foremost medical schools in Europe with a history of more than 200 years in training physicians and scientists. This history, however, is not so straightforward and undisturbed, so it is worth having a look at it.

Records indicate that medical training in Hungary occurred as early as the 13th and 14th centuries in universities of Buda, Pécs, and Pozsony (now Bratislava, Slovakia). During the 16th and 17th centuries, the Turkish occupation led to a decline in higher education in Hungary. The continuity is dated from 1635, when Péter Pázmány, archbishop of Esztergom, using mostly his private sources, founded the University of Nagyszombat in the northern, unoccupied part of Hungary. This university was supplemented by the establishment of a Medical Faculty by Queen and Empress Maria Theresia in 1769. A preceding imperial charter had promoted the whole institution to royal university status and endowed additional land grants to provide for the support of the new faculty. The scheme of the Medical Faculty at Nagyszombat was prepared by the court physician of the Queen (G. van Swieten), following the model of the Medical Faculty in Vienna that had also been reformed on the basis of his proposals. The building of the new faculty was designed by the famous architect Franz Anton Hildebrandt. In the beginning, education was carried out by five departments (anatomy, botany & chemistry, general pathology, physiology & pharmacology, and surgery). The lack of its own clinic, however, hindered the teaching until the University – together with the Medical Faculty – moved to Buda in 1777. Maria Theresia's son, Emperor Joseph the Second, ordered the move of the University to Pest in 1784; these were separate towns in that time.

Frequent moves blocked educational activities. The rapidly developing city of Pest, however, provided a richer and more varied patient population, and the number of departments, as well as that of the students increased steadily. Stricter regulations introduced by Joseph II on university examinations resulted in the mutual recognition of medical diplomas – at least of those issued in Vienna, Prague, Cracow, and Pest.

The dynamic life of the university at the turn of the century gave way to the retrograde influence of the age of Emperor Francis I. Nevertheless, as medical education was considered neutral to the ideas of French Revolution, medicine was the only faculty at the beginning of the 19th century where scientific activity or significant development was allowed. The list of outstanding scientists is not short and introduction of some new results preceded most European countries (e.g. immunisation against smallpox had been administered since 1799 in Hungary; the Institute of Pathology, founded in 1844, was among the earliest of such institutions; ether narcosis was introduced in early 1847 in Pest).

Instruction was given in national languages (Hungarian, German, Slovak) only at lower level courses: surgeon master, midwife, veterinarian. medical and surgical students, however, were instructed in Latin until the middle of the 19th century. A legal statute was enacted in 1830 to permit the use of Hungarian, and in 1844 Hungarian was adopted as the official language of medical education. Despite the patriotism of the professors, the Faculty had reservations, mainly because the special medical terminology had not yet been developed. Ultimately, Hungarian was introduced in 1848 as the language of medical education. After the defeat of the War of Independence, the freedom of teaching was also lost. From 1850, German became the official (and educational) language for ten years.

The history of the next 80-90 years is similar to that of most European institutions: quick and spectacular development on the one hand, restriction and even repeated catastrophes (two World Wars, the big economic crises, etc.) on the other. The number of students increased dramatically after WWII, and surpassed the capacity of the Faculty, so that a system of entrance examinations had to be introduced from 1947.

In 1950, Péter Pázmány University renounced its old name and adopted the name of Loránd Eötvös. The following year, the Council of Ministers promoted Hungarian medical faculties – not only in Budapest but in three other cities as well – to the status of independent universities. In 1955, two new faculties were incorporated into Budapest University of Medicine, as it was called in that time: Faculty of Dentistry and Faculty of Pharmacy. In 1969, on the occasion the bicentennial anniversary of the Medical Faculty, the name of the University was changed to Semmelweis University of Medicine. (Professor Ignaz Semmelweis was head of the obstetric clinic in Péter Pázmány University between 1855 and 1865.)

Presently the University has about 60 departments, several clinics with over 3500 beds, and about 2600, 700 and 600 students on the Faculties of Medicine, Dentistry and Pharmacy, respectively. About a quarter of the students are from abroad. University subjects are instructed also in German (since 1983) and in English (since 1988). A statistic about the scientific work at the University: 45% of the scientific publications from Hungarian universities are produced by the Semmelweis University of Medicine.

(continued...)

1996 Conference: Some More History

Ignaz Semmelweis (1818—1865)

Born in Buda in 1818, Ignaz Semmelweis was an eminent Hungarian obstetrician and a remarkable figure of medical science. He studied in Vienna and Pest, and after completing his M.D. degree, he specialized in surgery and obstetrics. Hebegan his career in the Obstetrics Clinic of the Medical School at Vienna. Concerned by the high rate of mortality following childbirth due to puerperal fever, he introduced antisepsis in 1847. This was most successful and the death rate was dramatically reduced from 18.2% to 1.2% as a result of his order to attending physicians to wash their hands in chlorinated water before all gynecological examinations or obstetrical deliveries. He came to the conclusion that puerperal fever is essentially similar to common sepsis and is not a contagious disease transmitted by the obstetrician.

Semmelweis' outstanding discovery was met, however, with constant misunderstanding and he finally returned to Budapest where, until his death in 1865, he continued to practice and to teach in his determination to reduce the perinatal mortality rate.

After leaving Vienna he worked in the St. Rókus Hospital in Budapest (now the Semmelweis Hospital). From 1855 onwards he was a Professor in the Medical School at Budapest.

Semmelweis published his findings in 1860 in his famous work: “The Aetiology, the Definition and the Prophylaxis of Puerperal Fever”. It is tragically ironic that Semmelweis himself contracted septicaemia and died of the disease he had spent his life trying to eradicate. His theory of asepsis was finally accepted by medical science some 20 years after his death. The Medical School of Budapest is named after him, and will host the 17th meeting of the ISCB in 1996.

ISCB News: News !

ISCB Changes of Address

Please inform the Vice-President who looks after money and also the membership and mailing list databases.

ISCB: The Future

Budapest 1996 and Boston 1997: please note announcements in this News.

1998-2000: Proposals for conferences for these years are now taking shape, with all candidates from Dundee, Trento and Heidelberg. If you have ideas about organising a future conference, the ExCom would be happy to receive them. Meetings in countries that have not hosted ISCB before would be particularly welcome.

ISCB ExCom

I realised just after the 2nd Barcelona ExCom meeting that the majority of the ExCom (8/13) will have finished their terms at Budapest and more importantly several may not be able to continue as they'll have finished 2nd terms (see below). Therefore there will be a need to recruit several new members. How about ***YOU*** ?

To summarise: Pr=President, PP=Past-President, VP=Vice-President, Tr=Treasurer, Se=Secretary, Ex=ExCom Ordinary Member, NC=NomCom, NL=NewsLetter Ed., OO=Other officer

Ex/Nom Com Member	Status
Karsten Schmidt	VP ends, Pr starts until 98
Marc Buyse	Pr ends, PP starts until 98
J;rgen Seldrup	PP ends, could be elected OO/Ex/leaves
Stephen Senn	2nd Se ends, could be elected OO/Ex/leaves
Bernhard Huitfledt	1st Tr ends, could be elected Tr/OO/Ex/leaves
Simon Day	2nd Ex ends, could be elected OO/leaves
Tony Johnson	2nd Ex ends, could be elected OO/leaves
Hans van Houwelingen	2nd Ex ends, could be elected OO/leaves
Maria Valsecchi	2nd Ex ends, could be elected OO/leaves (NC ends B96)
Bela Hajtman	1st Ex ends, could be elected OO/Ex/leaves
Nancy Geller	2nd Ex continues until Boston97
Albert Cobos	1st Ex continues until Boston97
David Warne	NL continues ...
Michael Schemper	NC continues until Boston97
Doug Altman	NC continues until 98

Barcelona Trip Report (or Statisticians in Shorts)

by ISCB's ranting reporter...

So, what was my first trip to Spain like ? Well, with the snow gently falling outside, it seems a long, long time ago now, back in the days when the French trains used to run past my window... let me see if I can jog my memory by trying to read some of the 49 pages of scribbled notes...

Shortly before going, I bought myself a small guidebook and was interested to read that the local people don't always speak the country's official language, but an ancient language called Catalan. Hmm, rather like Basel, perhaps, except that in this instance it turned out to be easier to read Catalan than Spanish, unlike Schwytzertüütsch which is much harder than German. So, what was promised ? "Barcelona is a sophisticated city where the creative energy of modern Europe and the seductive pleasures of the Mediterranean meet in happy unison. No one would ever call Barcelona provincial. It is definitely a capital, though now of a culture rather than a country. It may be the second city in Spain, but it is the heart and soul of Catalonia, and it ruled an empire before Spain was born". A week later, I think this was a good summary of what is now one of my favourite cities.

After a hard week's work in an exceedingly hot office, 35°C in the shade, it was a pleasant treat to reach a cooler climate on **Friday** evening. The flight was only 40 minutes along the winding Rhone valley and on towards the Mediterranean, and then a few circuits round Barcelona. A long walk to the railway station indicated that the humidity was rather higher than I was used to, but not as bad as northern Australia and Malaysia, thank goodness. The journey to the town centre in an ice-cold, air-conditioned train accompanied by classical music went smoothly as the station staff were happy to point the English speaking visitor in the right direction. A short walk to the hotel and it was time to plan the weekend's sight-seeing... An email from Guernsey McPearson had contained the warning that Barcelona was a "Hot, dangerous city at the wrong time of the year," so I decided to take extra care with my cameras, a warning that turned out to be prophetic (not for me, but for a friend and for another ExCom member).

A somewhat overcast **Saturday** saw me rushing round on the tube, trying to catch as many sights as possible. Being the beginning of August it was rather quiet, and it was difficult to believe that this was a city 10 times as big as the ones I'm used to. Having hosted the Olympic Games recently, the city has obviously benefitted tremendously, and is delight to explore. The tour started with the magnificent Camp Nou stadium, home of FC Barcelona, and continued with Estacio Sants, and then Placa Espanya. From there I walked towards the Palau Nacional, past the Font Montjuic, a magnificent set of fountains that play to music and coloured lights in the evenings. Then into town to see the harbour area and the statue of Columbus whose only connection with the city was that he returned here to be greeted by the Spanish King and Queen who had sponsored his adventure.

Sunday: even the rain couldn't spoil the wondrous Gaudi church, La Sagrada Familia, and a look at the architectural collection of building at Poble Espanyol, and then after the zoo (including the world's only albino gorilla), it was sunny at last and I arrived at the beach at Barceloneta. The ended with another stroll to the Arc de Triomf, and I returned to the hotel where the restaurant was now closed for the next month...

(continued...)

Barcelona Trip Report (part 2)

Monday: a look round the narrow winding streets near the Cathedral, along the Ramblas, through the Placa Reial, to the Placa Catalunya, and then another look round the harbour before returning to the University site for the 1st ExCom meeting. A familiar site greeted me: G. McPearson explaining to some young female statistician the intricacies of I don't know what... The meeting went smoothly, and we were pleased to discover that the meeting was over-subscribed. Other topics discussed were last year's meeting, future plans for meetings, the AGM, acquisition/disposition of funds, local groups, the News, SEDREG, and the constitution. The evening saw the Welcome Reception at a royal palace, set in beautiful gardens, and a pleasant time was spent learning about statistics Down Under with ISCB's chatty Aussie participants, followed by a trip to the shore at Barceloneta for "un helado", and a chat with a group of British statisticians, some of whom were busily colouring in the slides for their presentations the next day.

Tuesday: OK, now for a brief tour of the academic bit as all my academic colleagues have concentrated on the non-academic aspects of the conference. I'll not go into details, but just mention a few sessions and talks I particularly enjoyed. After the welcome address by President Marc Buyse, the 1st plenary session looked at ***Computer intensive methods in medical research***: *Reduction of bias due to model selection via resampling & cross-validation techniques* by Martin Schumacher (IMBI, Freiburg, Germany), and *Some recent developments in computer-intensive biostatistical methods* by Robert Tibshirani (Univ. Toronto, Canada), in which we learned about lassos and garrotes.

The next plenary was on the ***Analysis of repeated measurements***, and there were the following papers: *How to analyse change over time* by David Hand (The Open University, UK), who gave an interesting overview of statistical, mechanistic and stochastic approaches to modelling, *Linearly divergent treatment effects in clinical trials with repeated measures: efficient analysis using summary statistics* by Lars Frison (Astra Hassle, Molndal, Sweden), and *Models for multivariate binary data* by Juni Palmgren (Karolinska Univ., Stockholm, Sweden).

After a fine lunch with an ample supply of free water, I attended the first of several contributed paper sessions on ***Bayesian methods in clinical research (1)***: J.M. Grouin, B. Lecoutre: *Predictive probability for monitoring clinical trials*, Y. De Rycke, B. Asselain*: Bayesian analysis therapeutic trials with censored data*, J.E. Farebrother and S. G. Gilmour: *Response surface methods for clinical trials*, adapting ideas normally found in agricultural trials for use in drug trials, K. Abrams, B. Sanso: *Model discrimination in meta-analysis. a Bayesian prospective*, and D. Williamson, J. Whitehead: *Adaptive Bayesian methods in dose finding experiments*.

After a quick change of rooms and a look at the **Statistical modelling (1)** talk by J. Whitehead on *Sequential designs for equivalence studies*, including a comparison of the merits of PEST and EaSt, it was on to the ***Bayesian methods in clinical research (2)*** session: I. Albert, J.P. Jais: *Gibbs sampler for logistic model to analyse longitudinal binary data*, T.C. Smith, K.R. Abrams, D.R. Jones: *Hierarchical Bayesian approaches to the synthesis of evidence. the case of breast cancer screening*, J. Higgins, A. Whitehead: *Borrowing strength from external trials in a meta-analysis*, and L. Makris: *Predictive causality for adverse drug reactions*. It was fascinating to see how ideas first presented 2 or 3 years ago are now being applied by many statisticians who access to fast computers to do intensive computing with easy to use packages like BUGS.

The day ended with the formal ISCB dinner and a trip along the coast to near the resort of Sitges, and the excuse to don long trousers or skirts instead of shorts, and slightly more formal shirts. At least that's what most wore; the scruffy character from Basel who I remember seeing from year to year during my time there who turned up in trainers, jogging trousers and sweatshirt was obviously unaccustomed to attending statisticians' events. The food was OK, but the wine was an acquired taste, rather beyond my powers of acquisition. A stroll along the beach rounded off a pleasant evening.

Barcelona Trip Report (part 3)

Wednesday started with ***Statistical methods for the analysis of quality-of-life data***: *Development, validation and usage of a quality of life instrument* by Peter Fayers (MRC, Cambridge, UK), *Analysis of quality of life data: is there a need for a new methodology ?* by Manfred Olschewski (IMBI, Freiburg, Germany), and *The application of multi-level models to the analysis of repeated assessments of quality of life* by Simon Thompson (London School of Hygiene and Tropical Medicine, UK). Three excellent presentations on this increasingly topical subject.

Next came one of my 2 highlights of the conference: ***Statistical refereeing of medical journals***: Theodore Colton on *Statistical refereeing of medical journals*, D.G. Altman, S.N. Goodman, S.L. George: *Use of statistical reviewers by medical journals,* P.J. Kelly: *The statistical refereeing of biased studies in medicine: accept, revise or reject ?*, and C. Palmer, T. Johnson: *Statistical review - lessons from the Lancet*. Having only recently started reviewing papers for my new company, I've experienced how difficult it can be to provide helpful comments on the statistical content of medical papers. As more and more journals choose to have all their papers refereed by statisticians, more and more researchers will be turning to their statistical colleagues for help in preparing their manuscripts. The best journals also have produced guidelines to help authors produce good papers, and the ideas contained in these could be applied to papers in other journals. To list some of Ted's tips: avoid "numerical intimidation" of the reader, and when giving advice: be specific, substantiate changes, offer constructive not destructive comments, don't put down the author(s), avoid writing a summary of the paper, and if necessary, admit a lack of familiarity with particular techniques used.

After lunch, the ISCB faithful attended the AGM, and the day ended with an official trip round the old town. A good chance to see the parts I'd missed & a quick look at the Cathedral, & some of the attractive Gaudi buildings.

Thursday started with a plenary session on ***Latent variable models in biomedical research***: *Using the latent variable approach in developmental genetic epidemiology* by Andrew Pickles (Institute of Psychiatry, London, UK), *The use of latent variables for analysis of multiple outcomes in studies of birth defects* by Louise Ryan (Harvard School of Public, Boston, USA), and *Multi-sample analysis of measurement error models: issues on asymptotic robustness* by Albert Satorra (Univ. Pompeu Fabra, Barcelona, Spain). Next was ***Bayesian methods in clinical research***: *Model discrimination in meta-analysis: a Bayesian perspective* by Keith Abrams (Uni. Leicester, UK), *Applications of Bayesian methods in drug development* by Amy Racine Poon (Ciba, Basel, Switzerland), *& Bayesian procedures for asserting individual bioequivalence* by B. Lecoutre (C.N.R.S. and Univ. Rouen, France).

After meeting Lluis Jover in the conference Internet room, I saw ***Bayesian methods in clinical research (3)***: D.F. Heitjan on *Statistical considerations in intention-to-treat*, L. Gras, G. Doombos, S. Heisterkamp: *An empirical Bayesian method for estimating risk parameters in small populations*, S. Senn (!) *Statistical issues in project prioritisation in the pharmaceutical industry*, D. Faraggi, A Kramar, R. Simon on *Evaluating the importance of tumor markers using a Bayesian neural network for censored survival data*, & G.J. Manas: *Calculating the probability of paternity in genetic testing*, and ***Meta-analysis***: S.D. Walter: *Assessing the relationship between effect size and baseline risk in the context of meta-analysis*, S. Lewis: *Meta-analysis of case-control studies. unravelling the heterogeneity*, C. Frost, R. Clarke: *Dietary determinants of serum cholesterol levels: a meta analysis of the metabolic ward studies using multilevel models*, F. Boutitie, F. Gueyffier, S.J. Pocock, J.P. Boissel: *Analysis of change of the treatment effect over time in the framework of a meta-analysis.* The day ended with a glorious sunset over the Collserola hills, and a memorable return the colourful musical fountains at Placa Espanya.

Barcelona Trip Report (part 4)

Friday: Finally a chance to browse the bookstalls & excellent collection of posters. Each year the standards continue to improve, and of this year's crop, the winner of the £50 PSI prize was awarded to J.C. Bruce, A.V. Swan (PHLS Statistics Unit, London, UK) for their poster *The analysis of censored assay data*.

. The mini-symposium was on ***Methodological issues of prevention trials*** and was chaired by Mahesh Parmar (not only sockless like many presenters, but also sandal-less). Those attendees who'd already left missed the best session of the conference, as it would be difficult to find a better set of 7 speakers. *The US Tamoxifen breast cancer prevention trial* by Theodore Colton (Boston Univ., USA) and Carol Redmond (Univ. of Pittsburgh, USA) described the practical implications of what happens when something appears to go seriously wrong in a big trial: the impacts on and repercussions for the various people involved. *The UK Tamoxifen breast cancer prevention trial* by Jack Cuzick (ICRF, London, UK) which has now become international, and *Data monitoring in prevention trials* by Laurence Freedman (National Cancer Institute, Washington, USA) both concerned very large, very long trials which could produce important results about the health of many people.

After the break we had *Vaccine trials* by Peter Smith (London School of Hygiene and Tropical Medicine, UK, the only presenter all week attired in suit and tie !) and *The malaria vaccine trial* by Pedro Alonso (Hospital Clinic, Barcelona, Spain), *Asymptomatic HIV infection trials* by Michael Hughes (Harvard School of Public Health, Boston, USA), and *Trials in preventive cardiology* by Julie Buring (Boston Univ., USA)

And still it wasn't over as the ExCom had another meeting to attend before flying off home. We discussed a wide variety of topics: praise and a few complaints for the meeting, the PSI prize, next year's conference, how to proceed with adopting the new constitution, expenses, email addresses, future meetings: Budapest and Boston (and Trento (Italy), Dundee (Scotland) and Heidelberg (Germany) are looking increasingly more likely to be chosen for the years 1998-2000), insurance, etc. ...

A special mention must be made of Albert Cobos who masterminded the week and who joined the ExCom at the end after his election at the AGM. That tired, contented appearance was very similar to that of Simon Day 2 years before after he'd organised the Cambridge meeting. Congratulations once more for a magnificent job ! So, to summarise, a hot, sticky, entertaining, enjoyable week, the best of 3 ISCB meetings I've been to. I'm looking forward to Budapest in 1996, which promises to be just as good if not better.

I995 Conference LOC Chairman's Diary

by Albert Cobos, Barcelona, Spain

Those of you who attended the Conference Dinner during the ISCB16 meeting in Barcelona will remember I promised to organise a trial to test the Spanish wine we received from the hands of our President.

Indeed, I promised to organise a *k* period, 3 wine crossover trial to test the Spanish wine against both an active control, a French brand, and a placebo, an unknown brand, where *k* was to be a very large integer. More or less healthy volunteers were to be recruited among the Local Organising Committee (LOC).

Before a proper protocol could be agreed upon, many LOC members started assessing the study treatments at different time points, so that we ended up with a sort of sequential design. By the time I was finally prepared to perform the trial, not only had we already spent most of the overall significance level, but also most of the wines. Moreover, each volunteer self-administered the study treatments in a non-random, unblinded way, following different (random) designs.

Feeling that the validity of the trial was at risk, I decided to set up a data monitoring committee to take some fast decisions. After a successful alcohol-free meeting, the DMC reported the following conclusions:

- the trial to test wines was a complete mess, preventing us from reaching any serious conclusion regarding Spanish, French or other brands,
- the LOC realised the urgent need to repeat the experiment (a proper one), which is good news since it implies we can keep on drinking wine,
- to keep on drinking wine is consistent with the good memories we all in the LOC have of the Barcelona meeting, with its expected profit of about 3,000,000 ESP (= 16,000 GBP). We can only hope you share these feelings.

THE INTERNATIONAL SOCIETY FOR CLINICAL BIOSTATISTICS

The International Society for Clinical Biostatistics (ISCB) was founded in 1978 to stimulate research into the principles and methodology used in the design and analysis of clinical research and to increase the relevance of statistical theory to the real world of clinical medicine.

The ISCB organises an annual scientific meeting which members and non-members are able to attend. The main objective of the annual scientific meetings is to create an opportunity for the exchange of knowledge, experience and ideas among clinicians, statisticians and members of other disciplines, such as epidemiologists, clinical chemists and clinical pharmacologists, working or interested in, the field of clinical biostatistics.

The scientific meetings cover a broad spectrum of biostatistical interests and regularly include sessions on the design and analysis of clinical trials, epidemiology and statistical methodology, as well as from time to time considering more specialist issues such as, for example, education of biometricians and biometrics users, pharmacokinetics, medical data-bases and pharmacoepidemiology. Each meeting includes a mini-symposium devoted to a particular medical or statistical field. Recent examples have been Organ Transplantation, Regulatory Affairs in Europe and North America, Quality of Life, Statistics in Medical Journals, and Methodological Issues in Prevention Trials.

Previous meetings in recent years have been held in Cardiff (1986), Gothenburg (1987), Innsbruck (1988), Maastricht (1989), Nimes (1990), Brussels (1991), Copenhagen (1992). The 1993 meeting was held in Cambridge and Basel played host in 1994, with the last venue being Barcelona. Budapest in 1996 and Boston in 1997 will host the next conferences.

The proceedings of these scientific meetings are published in *Statistics in Medicine*. The ISCB benefits from a special journal concession from John Wiley & Sons Limited, the publishers of *Statistics in Medicine*, so that members are able to subscribe to the journal at a preferential rate of £150.

The ISCB also organises courses to cover particular statistical topics. These are run to precede or follow on from the annual scientific meeting and are given by the foremost researchers in the field. Recent courses have included Non Parametric Methods in Medical Research, Decision Analysis in Early Phase Drug Trials, Analysis of Longitudinal Data, Martingales in Survival Analysis, Issues in the Design of Clinical Trials, Sample Size Calculations in Clinical Trials, Overdispersion, Repeated Measures and Longitudinal Data, Analysis of Ordered Categorical Data, and Cross-over Trials in Clinical Research.

The annual general meeting of the ISCB is organised to coincide with the scientific meeting. Membership of the Society is drawn from over 30 countries worldwide and the number of members is over 700.

The current composition of the executive committee is as follows: President, Dr Marc Buyse (Belgium), Vice-President, Dr Karsten Schmidt (Denmark), Treasurer, Dr Bernhard Huitfeldt (Sweden), Honorary Secretary, Prof Stephen Senn (UK), Past President, Dr Jørgen Seldrup (UK), Newsletter Editor, Dr David Warne (Switzerland), and Members: Dr Albert Cobos (Spain), Simon Day (UK), Dr Nancy Geller (USA), Dr Bela Hajtman (Hungary), Professor Johannes van Houwelingen (Netherlands), Dr Anthony Johnson (UK), and Dr Maria Valsecchi (Italy).

The ISCB also has special working groups dealing with particular aspects of biostatistics. A particular focus in recent years has been statistics in drug regulatory affairs. The chairman of the ISCB working party on Statistics in European Drug Regulation (SEDREG) is Professor Wolfgang Köpcke, University of Münster, Germany. The other members of the SEDREG Executive Team are Drs Karsten Schmidt (Denmark) and Bernhard Huitfeldt (Sweden), and Professor David Jones (UK).

The Society publishes a newsletter twice a year. The editor is Dr David Warne, Chemin Frank-Thomas 32, CH-1208 Genève, Switzerland. Items for inclusion in the Newsletter should be sent to him (if possible on a 3.5" disk, Word6 format or text, or email on 100557.2260@compuserve.com).

Membership of the Society is open to all with an interest in biostatistics. The current annual (to 31 December 1995) Ordinary membership fee is £15. The Full-time Student Membership fee is £7.50. Members can also choose to receive Statistics in Medicine at a reduced cost (see above), and benefit from the reduced conference fee, at least £15 less than for non-members.

Applications for membership should be addressed to:

ISCB Permanent Office,
PO Box 25,
DK-3480 Fredensborg,
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Membership Subscription

INTERNATIONAL SOCIETY FOR CLINICAL BIOSTATISTICS

1996

Membership Subscription

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Business address _____ ☐ Medical Doctor

_____ ☐ Both

Post code and country _____ ☐ Neither

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	☐	£	165.00	Ordinary Membership of ISCB (to December 31, 1996) + subscription to *Statistics in Medicine,* 1996.

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Please return this form to: **ISCB Permanent Office, P.O. Box 25, DK-3480 Fredensborg, Denmark, Tel: +45 42 284100, Fax: +45 42 284200.**

Calendar

27-30 May 1996 — **Quebec, CANADA**

28th Journées de Statistique (with Société Française de Biométrie)
Info: J-P Carmichael, Dep't de mathématiques et de Statistique, Université Laval, Sainte-Foy, Quebec G1K 7P4, Canada
Tel: +1 418 656 2973, Fax: +1 418 656 2817, email: asu96@mat.laval.ca

6-10 July 1997 — **Boston, USA**

ISCB18 (Joint meeting with Society for Clinical Trials)
Info: Laurence Freedman (National Cancer Institute, Biometry Branch, DCPC, 6130 Executive Boulevard, MSC 7354, EPN Room 344, Bethesda MD 20892-7354, USA.
Tel: +1 496 7748, Fax: +1 301 402 0816, email: l3f@cu.nih.gov
email: compstat@eio.upc.es, WWW: http://sunrai.upc.es/compstat

8-12 July 1996 — **Sydney, AUSTRALIA**

13th Australian Statistical Conference
Info: Director SISC-96, CSIRO Div. of Maths & Stats, Locked Bag 17, North Ryde, NSW 2113, Australia
Tel: +61 2 325 3256, Fax: +61 2 325 3243, email: sydney96@syd.dms.csiro.au,
WWW: http://www.dms.csiro.au/sisc/

15-19 July 1996 — **Orvieto, ITALY**

11th International Workshop on Statistical Modelling
Info: Dipartimento di Scienze Statistiche, Universita' di Perugia, via A.Pascoli, Casella Postale 1315/PG1, I-06100 Perugia, ITALY
Tel: +39 75 585-5227, Fax: +39 75 43-242, email: wks96@stat.unipg.it,
WWW: http://www.stat.unipg.it/iasc/iwsm11.html

16-18 July 1996 — **Leicester, ENGLAND-UK**

Statistical Issues in Biopharmaceutical Environments
Info: Prof. B. Jones, Dep't of Med. Stats, School of Computing Sciences, De Montfort University, The Gateway, Leicester LE1 9BH, ENGLAND-UK
Fax: +44 116 254 1891, email: bj@dmu.ac.uk

19-22 August 1996 — **Copenhagen, DENMARK**

13th International Congress of Medical Informatics Europe (MIE96)
Info: MIE96 c/o DIS Congress Service Copenhagen A/S, Herlev Ringvej 2c, DK-2730 Herlev, Denmark
Tel: +45 44 924492, Fax: +45 44 925050, email: mie96@risoe.dk,
WWW: http://www.risoe.dk/mie96.html

26-30 August 1996 — **Barcelona, SPAIN**

COMPSTAT'96
Info: Prof. Dr. A. Prat, Dpt. d'Estadistica i Inv. Operativa, UNIVERSITAT POLITECNICA DE CATALUNYA, Av. Diagonal, 647, E-08028 BARCELONA, SPAIN
Tel: +34 3 4016569, Fax: +34 3 4016575,

16-19 September 1996 — **Wroclaw, POLAND**

26th International Biometrical Colloquium
Info: S. Mejza, Agric. University of Poznan, Wojska Polskiego 28, PL-60637, Poland
Fax: +48 61 487145/6, email: smejza@au.poznan.pl

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