International Society for Clinical Biostatistics News

Number 22 April 1997 Editor: David W. Warne

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Editorial

It's the end of April and now only 2 months to wait until ISCB's first joint meeting with SCT across the Atlantic, in Boston. You should by now have received the exciting preliminary programme, packed with interesting talks and things to do when not at the conference. With no les than 5 parallel sessions, advanced planning is called for, so do have a look at the programme before you arrive in Boston, perhaps during the long flight.

In this News, you'll find the usual mixture of contributiions from various countries. I do hope you'll be inspired to write something interesting and have the courage to send it to me - amusing trip reports are alwas very welcome.

Thanks to the contributors to this News: Karsten Schmidt, Simon Day, Nancy Geller, Andrew Lawson, Albert Kandra, Elisabeth Wehrle, Insa Gathmann, Albert Cobos, Anna Bartkowiak, Joe Shih, Julia Singer, Stephen Senn and Bernhard Huitfeldt.

Note that it is planned to publish ISCB News twice more in 1997, August/September and December. Deadlines are mid-August and mid-November, respectively.

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ISCB Membership

Please note that if you attended the Budapest meeting but haven't renewed your ISCB subscription for 1997, your membership ends with this News, and you will have to pay the non-member's fee for Boston.

		Maastricht		Brussels		Cambridge		Basel		Barcelona		Budapest			Boston
		ISCB10	end	ISCB12	end	ISCB14	Dec	ISCB15	Dec	ISCB16	Dec	ISCB17	Dec	Apr	Jul
		Sep89	89	Jul91	92	Sep93	93	Jul94	94	Jul95	95	Jul96	96	97	97
	Total	276	261	859	596	377	715	305	698	425	725	283	702	434	?
	# Countries	19	23	30	32	27	32	22	31	30	33	26	34	32	?
#	Country														
1	UK	33	50	86	90	128	176	51	120	98	144	44	121	88	
2	Germany	39	30	80	67	39	75	42	84	23	71	35	78	51	
3	Sweden	14	23	37	51	22	53	20	54	37	58	19	64	39	
4	France	29	30	78	52	26	62	21	50	46	73	29	67	37	
5	USA	13	18	227	45	16	40	14	39	25	41	21	40	37	
6	Poland	1		3	11	2	11	4	24	2	24	7	30	*	
7	Belgium	5	13	99	22	13	27	13	30	14	30	8	32	25	
8	Hungary		1	4	21	1	17	4	18	6	19	25	25	*	
9	Netherlands	94	14	46	30	23	38	22	33	23	36	10	29	22	
10	Switzerland	10	14	24	25	8	22	68	80	14	33	10	29	22	
11	Italy	11	16	47	33	23	37	8	32	13	32	18	33	21	
12	Denmark	3	4	14	58	23	38	8	31	16	30	11	32	19	
13	Austria	7	4	4	9	6	11	6	13	4	11	9	16	11	
14	Spain		10	14	12	9	18	6	12	71	46	7	23	10	
15	Canada	3	6	35	12	5	14	6	14	4	11	4	13	8	
16	Norway	4	13	17	18	10	25	3	22	3	12	10	18	7	
17	Australia	2	6	12	9	2	11		6	3	9		8	7	
18	Japan	3	2	10	6	4	7	1	5	2	7		4	4	
19	Finland	3	2	4	7	4	7	2	9	3	9	2	9	3	
20	Ireland	1	1	1	2	1	3		4	4	3	1	4	3	
21	Russia									1	1	2	3	3	
22	Hong Kong				1		1		2	2	3	1	3	3	
23	Israel		1	3	3	3	4	3	4	1	4	3	4	2	
24	Portugal		1	4	3	2	5		2		2		2	2	
25	South Africa				1	3	4		1	1	3		2	2	
26	New Zealand				1			1	1			2	2	1	
27	Thailand			2	1		1			1	1	1	1	1	
28	Iran									1		1	1	1	
29	Czech. Rep.						1		1		1		1	1	
30	India	1		1	1		1		1		1		1	1	
31	Malaysia										2		1	1	
32	Mexico			1									1	1	
33	Indonesia													1	
34	Romania											2	2		
35	Slovenia			1	1	1	2	1	3	1	2	1	1		
36	China				1	1	1		1		1		1		
37	South Korea									3	3				
38	Brazil									2	2				
39	Cuba									1					
40	Greece				1	1	1	1	1						
41	Zimbabwe								1						
42	Kenya			2	1	1	1								
43	Turkey			1	1		1								
44	Columbia			1											
45	Philippines			1											
46	Kuwait		1												
47	Oman		1												

* see ISCB Local Groups.

ICH Guidelines on Biostatistics II

by Bernhard Huitfeldt

One year ago I reported in our Newsletter on work on the ICH Guidelines on Biostatistics. At that time the Expert Working Group had had its first meeting in Washington and the position of the six involved parties had been elucidated. Once we had agreed on the level of detail, i.e. principles rather than procedures, no major disagreements on statistical matters were revealed. Considerable rewriting of selected parts of the base document (CPMP guidelines) was initiated and the results of this were discussed at a meeting in Tokyo at the end of August 1996.

This was the first time that we were confronted with new committed formulations. At this stage it was evident that there existed regional differences in emphasis on topics. For example, global assessments and the role of placebo-controlled trials are very important for the Japanese region, whereas bias and robustness issues are emphasised in the US. In Europe, multicentre trials, equivalence trials and the blind pre-analysis review of data are of great interest.

After the Tokyo meeting, the first consolidated version of the new guidelines was compiled, and this was discussed at the last EWG meeting in London in early November. It was obvious from this draft that it is not an easy matter to revise a well-worked out and homogenous document (CPMP guidelines) by chopping it into pieces, adding, removing, rewriting things here and there, and putting it together again. Not surprisingly, it no longer gave the impression of a well-worked out and homogeneous document. Considerable editorial work was required at this stage in addition to solving a couple of outstanding issues.

Anyway, it was possible to reach a step 2 document of the ICH process which was signed off by the EWG on 16 January this year. The document is now out for a step 3 consultation, the result of which will be discussed by the EWG at the ICH-4 meeting in Brussels in July this year. It is still the ambition to reach step 4 immediately after that meeting, which would imply an implementation by the turn of the year.

It has been an exciting and rewarding experience to take part in this work. Among other things, to participate in the establishment of a common view on statistical principles for clinical trials in a major part of the world, and to put these in one place for everybody to assimilate has been interesting. And to cooperate with colleagues from all over the world and make new acquaintances is always fascinating.

Permuted Blocks with Mathcad 6.0 Plus

by Stephen Senn

One of the advantages of being an applied statistician working in the pharmaceutical industry is the degree of professional support which you can obtain. This is not always available to the same degree elsewhere. This was brought home to me the other day when at the statistics clinic which we run here at UCL, a client asked me to produce a randomisation list for a trial to be run in permuted blocks. In the days when I worked for CIBA-Geigy, I frequently ran such trials but all that it was necessary for me to do was to specify the block length, the treatments and the numbers of patients. The list was then produced by the trial logistics department. With no such resource to fall back on now I began thinking as to what was the most efficient way to do this. (Efficient for me, that is. I am not too concerned about saving the PC's time.)

My first thought was that given a block of length k with two treatments, I would need to identify all possible permutations with k/2 of each treatment and then choose the blocks so identified at random. This looked to be rather tedious. And I looked for alternatives. It then occurred to me that the median of a sample has the property that exactly half the numbers are greater than it and half are smaller. Thus, if a series of uniform independent numbers were generated at random and coded according to whether they were above or below the median, this would be equivalent to choosing a possible permuted block at random. This is something that can be done very easily with Mathcad and I thought that readers of ISCB News might like to see how. In fact, this whole article is written in Mathcad and the program follows below after some introductory notes.

To produce a randomisation list for a placebo controlled trial of an active treatment with permuted blocks using Mathcad 6.0 Plus.

n is the number of patients
k is the number of patients per block
b is the number of blocks
1 is an active treatment
0 is a placebo
Treat is the matrix of permuted blocks

Notes

Φ(x) is the Heaviside function and returns a 1 if x is greater than or equal to zero and a 0 if the argument is negative.

rnd(x) is a function which returns a random number distributed uniformly between 0 and x

ceil(x) rounds x up to the nearest whole number

median(V) calculates the median of a vector, V, of observations

The built in variable ORIGIN has been set to 1 so that the first row of any matrix is row 1 and so forth.

submatrix(A,ra,rb,cx,cy) extracts a submatrix of an original matrix and consists of rows ra to rb and columns cx to cy.

Begin program

Set parameters

$n := 150 \quad k := 10$

Calculate number of blocks

$b := \mathrm{ceil}\left(\frac{n}{k}\right) \quad b = 15$

The ceil function is used to round up just in case the number of patients is not divisible by the block length.

Generate random numbers. (i is the block subscript, j is the subscript for the patient within blocks.)

$i := 1, 2 .. b \quad j := 1, 2 .. k \quad \mathrm{Uniform}_{i,j} := \mathrm{rnd}(1)$

Uniform is now a b x k matrix of uniform random numbers. If we subtract from each value in a row, the row median, half of the resulting values will be negative and half will be positive. If we then apply the Heaviside function, half of the values will be 0 and half will be 1. We shall then have a set of treatment codes with the desired properties. To do this we need to use three functions: submatrix, median and Φ(.).

$\mathrm{Treat}_{i,j} := \Phi\left(\mathrm{Uniform}_{i,j} - \mathrm{median}(\mathrm{submatrix}(\mathrm{Uniform}, i, i, 1, k))\right)$

Permuted Blocks with Mathcad 6.0 Plus (continued)

Now let us check that the values of Treat have the desired property. Each row should have a mean of exactly 0.5. Hence, the mean of all the row means should 0.5 and the variance should be 0. Let us create a variable checkr to examine this. Although the mean of a given column does not have to be 0.5, the mean of these means does and the mean of the variance of the columns should be approximately 0.25. Let us create the variables checkc and checkcv to examine this.

$checkr_i := mean(submatrix(Treat, i, i, 1, k))$

$mean(checkr) = 0.5 \quad var(checkr) = 0$

$checkc_j := mean(submatrix(Treat, 1, b, j, j))$

$mean(checkc) = 0.5 \quad mean(checkcv) = 0.2311$

$checkcv_j := var(submatrix(Treat, 1, b, j, j))$

Finally, let us print out the permuted blocks

Treat =

	1	2	3	4	5	6	7	8	9	10
1	0	0	1	1	1	0	1	1	0	0
2	1	0	0	1	1	0	0	0	1	1
3	1	1	0	0	1	0	1	0	0	1
4	0	1	0	0	1	1	0	1	0	1
5	1	1	1	0	0	0	1	0	0	1
6	0	0	1	1	1	0	1	0	1	0
7	1	0	1	1	0	1	0	0	1	0
8	0	1	0	1	1	0	1	0	0	1
9	0	1	1	1	0	0	0	0	1	1
10	0	0	1	0	1	0	1	1	0	1
11	0	1	1	1	1	0	0	1	0	0
12	1	1	0	0	1	0	0	1	1	0
13	0	0	0	1	1	0	1	1	1	0
14	1	1	1	0	0	0	1	0	0	1
15	1	0	0	0	1	1	1	0	0	1

And there we have it: random permuted blocks.

Computer Corner

"My computer's too fast !" Never thought I'd have to admit it, but now SAS runs so quickly I can't even read the log as it scrolls past. So it can't be long until new versions of the software catch up in complexity and I'll need an even faster PC to cope...

This month has been busy for me, filling in an electronic CRF. Not for a clinical trial (we're working on that) but for my annual tax return. The challenge of doing this in French for the first time was somewhat reduced by the prospect of filling in the numbers in Excel and sending in a diskette to the inspectors rather than doing all the work on paper. I'll see how it turns out in the autumn... how long until all our personal info will be linked on the www and filling in forms will be a thing of the past ?

If you've an event to announce, but the ISCB News publishing dates (April, August/September and December in 1997) aren't convenient, it will be possible to add something to mention your course or congress on the web homepage. Please contact the editor for details.

Articles sent via email or on diskette (Word6, WordPerfect or text) on almost any topic are most welcome. This is an informal newsletter for you the readers, so please join in and make ISCB News a magazine that's even more interesting and fun to read.

ISCB

ISCB Subcommittees

Please contact the chairmen of these subcommittees for further information.

Title	Terms of Reference	Members
SEDREG (Statistics in European Drug Regulation)	The terms of references and function for the SEDREG SubCommittee is to finalise as soon as possible the position paper being prepared by the former Executive Team members. A final edition of the paper approved by the Committee must be available before the end of 1996 at which time the SubCommittee should be disabled.	The SubCommittee is chaired by Prof. Wolfgang Köpcke of the University of Münster (Germany), Prof. David Jones of the University of Leicester (UK) serves as Secretary, and Dr Bernhard Huitfeldt of Astra Arcus AB (Sweden) and ISCB's President Dr Karsten Schmidt of Spadille Biostatistics ApS (Denmark) are members.
Fraud	The SubCommittee on fraud will have the following goals: 1. to investigate the role of biostatistics in the prevention and detection of fraud in clinical research, and 2. to promote the role of appropriate biostatistical contributions in the assessment of misconduct. The SubCommittee will produce a position paper reflecting the opinions of its members. A manuscript will be available prior to, or at the next meeting of, the ISCB. The SubCommittee will coordinate its efforts with those of the Society for Clinical Trials, which is developing a paper on data integrity. The name of the SubCommittee may have to be changed as a result of its deliberations, as the term "fraud" may have legal implications.	Chair: Dr Marc Buyse, Brussels (Belgium), Secretary: Dr Jane L. Hutton, Newcastle upon Tyne (UK), Dr Lutz Edler, Heidelberg (Germany), Prof. Stephan Evans, London (UK), Dr Nancy Geller, Bethesda (USA), Prof. Stephen L. George, Durham (USA), Prof. Emmanuel Lesaffre, Leuven (Belgium), Prof. Gordon Murray, Glasgow (UK), Dr Jonas Ranstam, Lund (Sweden), Dr Bruno Scherrer, Fresnes (France)
Statistics in Regulatory Affairs	The SubCommittee on Statistics in Regulatory Affairs will consider and influence the development of regulatory requirements, guidelines and other documents concerning the scientific aspects of data collection, management, analysis, and reporting. Also the SubCommittee will work on issuing new guidelines on these topics, where it is needed. The SubCommittee will serve for four years at which time its existence may be reapproved subject to clause 7.08 of article 7 in the Constitution.	The SubCommittee is chaired by Prof. Helmut Schäfer of Institute of Medical Biometry, Marburg (Germany), Prof. Stephen Senn of University College London (UK) serves as Secretary, and Dr Jørgen Seldrup of Quintiles S.A. Strasbourg (France), and ISCB's President, Dr Karsten Schmidt of Spadille Biostatistics ApS (Denmark), are members.
Education	The SubCommittee on Education will assess the feasibility of organising a one or two day course on contemporary methods in Clinical Biostatistics which will involve several members as lecturers and be presented in locations represented by the Society. This includes assessment of costs and organisation of such a course. Once feasibility has been assessed, this sub-committee will be responsible for planning the course curriculum and selecting lecturers. The financial role of ISCB should be considered. The sub-committee will also receive requests from members that this course be given at their location and evaluate them. The first site at which the course will be presented is Barcelona, Spain from 25-27 June 1997 on the topic "Design and Analysis of Cross-over Clinical Trials" by Stephen Senn.	Chairman: Dr Mike Campbell (UK) Members: Dr Nancy Geller (USA) and Dr Albert Cobos (E)

Notice of ISCB AGM

from Simon Day

Notice of a General Meeting of the Society

The Annual General Meeting of the International Society for Clinical Biostatistics will be held at the conference site in Boston from 12.15 to 13.45 on Wednesday 9 July 1997.

Nominations are invited for:
1 place on the Executive Committee for 1998-99, for which a postal ballot will be held later in the year.

Nominations for the committee and items for the agenda may be communicated to the Secretary of the Society, Simon Day as follows:

Simon Day, Secretary ISCB
LEO Pharmaceuticals, Longwick Road, Princes Risborough, Bucks. HP27 9RR, England-UK
Tel: +44 1844 347333
Fax: +44 1844 346088

ISCB Aims

The Society is organised and shall be operated for educational and scientific purposes with the following Aims:

- to stimulate research on the biostatistical principles and methodology used in clinical research;
- to increase the relevance of statistical theory to clinical medicine;
- to promote high and harmonised standards of statistical practice;
- to work with other societies and organizations in the advancement of biostatistics;
- to promote better understanding of the use and interpretation of biostatistics by the general public, and by national and international organizations and agencies within the public and commercial sectors with an interest in, and/or responsibilities for, public health; and
- to provide a common forum for clinicians and statisticians through meetings, seminars and publications.

Advertising Rates

The new costs are: **Full A4 page: £ 200** **Half A4 page: £ 150** **Quarter A4 page: £ 100**	**Additionally, we will include loose flyers with the distribution of the newsletter at an initial handling cost of £ 150. However, if the addition of the flyers increases the postal charges, the advertiser will also be charged the difference in distribution costs. For further information, please contact the Editor.**
Publishing dates in 1997:	**August/September and December**
Deadlines:	**mid-August and mid-November**

ISCB 19 - Dundee 98

by Andrew Lawson

The annual conference of the International Society for Clinical Biostatistics is to be held in Dundee UK
on **24th-28th August 1998**.

The **venue** is the Stakis Dundee conference centre in the heart of the city. This venue boasts a waterfront location and is close to all central amenities.

Dundee is well placed as a central location for visiting many Scottish tourist attractions: e.g. Edinburgh (1h), Glasgow (1.5h), Aberdeen (1h), and beautiful highland glens (45m).

The **local organiser** of the conference is Dr Andrew Lawson, and the **Scientific Committee** consists of:

Gillian Raab (UK) (**Scientific Chair**)
Andrew B Lawson (UK) (**Local Chair**)
Emmanuel Lesaffre (B)
Frank Rockhold (USA)
Gordon Murray (UK)
James Urquart (USA)
Jane Hutton (UK)
Martin Kulldorff (USA)
Niels Keiding (DK)
Siem Heisterkamp (NL)
Sylvia Richardson (F)
Willi Sauerbrei (D)

A programme of **invited sessions** has been organised and these are:

Clinical Trials
Meta-analysis of screening
Infectious Diseases (excluding Aids)
Modelling Uncertainty /
Prognostic Modelling
Missing Data

There will also be a **mini-symposium** on:
Environmental Epidemiology

A number of courses and workshops will also be a feature of this conference, and there will be a variety of **contributed paper** and **poster** sessions.

Currently, a preliminary brochure is under development and will be available by July 1997.

Any further enquiries concerning the Conference can be directed to:

CEP Consultants LTD
43 Manor Place
Edinburgh
EH3 7EB
Scotland-UK.

tel: +44 131 300 3300
fax: +44 131 300 3400

Informal enquiries about the scientific programme can be directed to myself:
Andrew B. Lawson
email: a.lawson@tay.ac.uk
tel: +44 1382 308604

One special feature of this meeting is that it's being planned early enough for us to issue the following:

"Call for Topics "

Yes, what would **you** like see as a topic at an ISCB meeting ?
Please send your suggestions to me, Andrew Lawson.

Design and Analysis of Cross-over Clinical Trials

by Stephen Senn

25-27 June 1997
Barcelona, Spain

with the support of the Dep. de Salut Pública i LS,
Facultat de Medicina, Universitat de Barcelona

Course contents

The course will include lectures as well as 'hands on' computer exercises using SAS. The course will cover the following topics:

Wednesday 25

AM - Introduction and a simple example

PM - The problem of carry-over

Thursday 26

AM - Non-parametric analyses, binary data and special designs

PM - Designs with three or more treatments

Friday 27

AM - Planning issues including a case study: an incomplete blocks design in seven treatments and five periods

PM - Adjusting for carry-over

Speaker

Professor Stephen Senn
Department of Statistical Science &
Department of Epidemiology and Public Health
University College London

Stephen Senn has a long experience in the field of clinical trials from the pharmaceutical industry perspective and is author of a well known text book on Cross-over trials.

Who should attend

The course is tailored to the needs of applied statisticians and medical researchers who wish to understand the statistical concepts relevant to the design and analysis of cross-over trials and to carry out analyses of such designs using SAS.
Participants should be familiar with SAS before attending the course.

Venue

The course will be held at the Faculty of Medicine, University of Barcelona (143 Casanova Street).

Fees

The course fee is 45 000 ptas for early registrations (before 25 May) and 55 000 ptas for late registrations. This includes course materials, coffees and lunches for all three days.

Registration and further information

Registrations will be restricted to 30 participants and will be accepted on a first-come, first-served basis. Please, complete the enclosed Registration Form and send or fax it to:

Albert Cobos
Novartis Farmacéutica, S.A.
Gran Vía de les Corts Catalanes, 764
E-08013 Barcelona, Spain
tel: +34 3 306 44 08 fax: +34 3 265 17 06 e-mail: Alberto.Cobos@Pharma.Novartis.com

(In case of low registrations the course might be cancelled. In this case, those who have registered will be so informed and registration fees will be fully refunded.)

Advert: Euromedica/Novartis

Announcement: ASU Biopharmacie 97

ISCB 17 - Budapest 96

by Insa Gathmann, Albert Kandra and Elisabeth Wehrle, CH.

Pre-Conference course: Extending the Cox Model by Terry Therneau (Mayo Clinic, Minnesota, USA)

This one day course about the Cox Model was very interesting and especially useful for those of us working in the cancer area. The main new issues were the discussion of multiple events, general censoring, time dependent covariates and residual plots. Terry gave good examples with more emphasis on S-Plus rather than SAS. It is more flexible, powerful, significantly better for survival and more user friendly for graphics. SAS was mainly used for data manipulation; S-Plus more for analysis. However, the venue of this course was not so excellent as the room was totally overloaded by a factor of 2 with the consequence that the air-conditioning could not handle the outside temperature of 30°C together with the additional heat produced by the 60 participants and the incredible over-heat' projector from the Russian production around 1950.
The most useful words were:

"All models are wrong but some are useful"

and

"You don't have to be completely correct as long as you are not stupid"

Conference from 26-29 August 1996: The topics were: 1) Philosophy, Past and Future of Clinical Biometrics and Philosophy and Clinical Aspects, 2) Graphical Methods in Clinical Research, 3) Philosophy, 4) Statistical Methods, 5) Issues in Clinical Trials, 6) Age-Related Percentiles and Growth Curves, 7) Repeated Measures, 8) Explained variation, 9) Disease Clustering and Geographical Analysis, 10) Survival Analysis, 11) ROC and Reliability, 12) Health Care Assessment and Pharmaco-Economics, 13) Genetics, 14) Methods in Clinical Research, 15) Public Health and Miscellany. There were lots of different talks in each of the topics mentioned above, but to be honest, none of them was really relevant for our daily work. However, we'll pick out some highlights.

A lively discussion came up about the relevance and usefulness of R^2. Stephen Senn during the coffee break after the talk to us: "Did you ever use such strange and perverse measure like the R^2 ?".

Most of the topics were not relevant for clinical biometricians as they were more general research of single people in their area of work, mostly not working in a pharmaceutical company. The only speaker who really knew the link between statistics and the "real pharma world" was again Stephen.... Every speaker got "cold feet" when Stephen stood up after the talk to ask a question or even worse... if he made a comment.

The future of biostatistics: expecting the unexpected: HC van Houwelingen (NL)

The nightmares presented in his talk: The mouse-click for the choice of a picture which looks best without thinking which one is the most appropriate. Statistics should be science and not art.
Other Nightmares: p-values; rank tests (without given estimate effect); exact methods (sampling scheme not known) and meta analysis (poor man's solution)
His Dreams: Instantaneous Integration (he meant Pseudo Likelihood and GEE for estimation of parameters).
Dream 2: Incorporation of follow up data in the protocol. The old fashioned meta analysis could be avoided.
Dream 3: Disease mapping based on the spatial correlation of the effects in space and time (no further specifications or examples were given).
Tremendous applause... and everybody is using more p-values....

New approaches for evaluating safety data: L Edler (D)
He proposed three methods for the analysis of safety data:
1) Semi-Markov Models
2) Time to toxicity proportional hazard models
3) Longitudinal model with an example of a GEE model in an adjuvant chemotherapy trial in colorectal cancer... so it's time to change our "standard" programs...

The use of auxiliary events to improve analysis of survival: P Flandre (F)
A parametric approach was presented using auxiliary information e.g. CD4 counts <200 cells/mm3 to estimate the survival function. Methods from Lagakos (1976) and Finkelstein and Schoenfeld (1995) were presented. After taking account of the auxiliary event information, age showed a significant effect in the model, whereas there was no effect before.

Statistical methods for economic evaluations of health care: FE Harrell (USA)
Costs of follow-up hospitalisations have a skewed distribution and many patients may have zero costs. This was the motivation for the use of a Cox semiparametric regression. The model was used for predicting follow-up charges for patients. In conclusion it was found flexible, robust and solves distributional problems associated with highly skewed data.

An application of Bayesian decision theory to phase II trials: N Stallard (UK)
Bayesian decision theory was used to choose a design to maximise the prior expected value of some specified gain function. He proposed

n.k	fixed costs in phase II for each patient
m	costs of Phase III
R-λn	Reward for success (discounted)

The approach was to go to phase III on model costs and gains, i.e. one is more interested in the right decision than in hypotheses testing. Solutions were presented for three cases:
1. The trial has a fixed sample size with final decision either to proceed in phase III or to reject the new treatment (Brunier and Whitehead 1994)
2. A single interim analysis with opportunity to proceed to a phase III trial, to reject treatment or to treat a further (fixed) number of patients.
3. Fully sequential design with a decision after each patient to proceed with phase II or to proceed with a phase III trial. This problem was addressed by Thall and Simon (1994), although their designs are not chosen to be optimal with reference to a stated gain function.
In conclusion 3) seemed to be universally optimal although the use of a single interim analysis yields almost as much gain in the presented example. In general the decision theory enables the choice of an optimal design. During the discussion it was criticised that all models are uncertain because they are working with a pre-specified response, e.g. from historical data which is not true for the study population.

The poster session included topics on graphical methods, incomplete observations and again meta-analysis

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Budapest was nice and interesting, we had a beautiful boat-trip in the evening (where Stephen had to decide between a long chat with a good looking Swedish woman and the dessert buffet and finally ended up with neither). Further, it was nice to meet other people from pharmaceutical companies and universities.

Overall, the pre-conference course was very useful and the congress was good. The program for the ISCB in Boston next year was shown - there seem to be many more useful topics.

ISCB Local Groups

from Jorgen Seldrup

The (new) ISCB Constitution, adopted by the General Meeting in Budapest in August 1996, provides for the setting up of National Groups. In Article 8.01 it reads:

> "*The Committee* may recommend the establishment of National Groups in countries where there are exchange control restrictions or barriers. Formal proposals for the formation of National Groups, including details of concessions, funding and banking, as well as for the use of these funds, must be prepared by *The Committee* in discussion with *Members* from those countries, and approved by postal ballot by majority vote of at least two-thirds of those voting. The National Group will be formally recognised six months after the vote of approval subject to there being at least two *Members* and the setting-up of the agreed financial arrangements."

Following discussions with ISCB members in Poland and Hungary, in particular with Witold Kupsc from Poland and Bela Hajtman from Hungary, *The Committee* has prepared the following information as a background to a proposal for the formation of a

Polish National Group

In 1990 ten Polish members of the ISCB grouped informally under the leadership of Ewa Krusinska, who remained the spokesperson for the group until 1993. Since then Witold Kupsc has represented the interests of the Polish members. Since 1990 the membership has grown steadily and stood in 1996 at 30 members. Over the same period a varying number of members have attended and presented at ISCB meetings, often with support from the Society.

In June 1994 a seminar on "Statistics in Clinical Practice", repeated in 1996, was organised in Warsaw by the Centre for Postgraduate Medical Training in collaboration with the Polish Group members of the ISCB. In October 1994 the group again collaborated, this time with the National Institute of Cardiology in Warsaw and the University of North Carolina in USA, to present a course on "Biostatistics and Epidemiology".

The membership fee for Polish members is currently 10 PLZ (around 3 to 4 $US). These monies have since 1993 been kept in a bank account with the Polish Biometric Society (in 1993 bank charges grew dramatically in Poland and The Group made the current arrangements with the Biometric Society).

In addition to financial support from The Society for members' attendance at ISCB meetings, one copy of "Statistics in Medicine" was also made available for circulation amongst members free of charge (in collaboration with the publishers John Wiley & Sons).

and a

Hungarian National Group

A Hungarian group of ISCB members, 17 in all, was formed in February 1991 by Bela Hajtman, encouraged by the then President, Wolfgang Koepcke. In 1996 the number of ISCB members in Hungary had grown to 25, helped by the fact that, that year the ISCB's Annual Conference was held in Budapest. Over the same period a varying number of members have attended and presented at ISCB meetings often with support from the Society.

Over the years this group, known locally as the Hungarian Society for Clinical Biostatistics, have been having regular meetings and incidental courses. In 1992/93 the group, still with Bela as spokesperson, offered to arrange a future ISCB conference in Hungary, and 1996 was targeted, as that would be the year, when the World Exhibition would be held in Hungary. Well, the World Exhibition did not happen, but the ISCB held a very successful meeting at the Semmelweis University, organised by a handful of dedicated ISCB members.

The current membership fee is 1200 HUF (approximately 7-8 $US), having increased from the original 1000 HUF some three years ago. However, at that time 1000 HUF were worth about 12 $US. Income from membership fees is held in a separate ISCB account in Hungary.

In addition to financial support from The Society for members' attendance at ISCB meetings, one copy of "Statistics in Medicine" was also made available for circulation amongst members free of charge (in collaboration with the publishers John Wiley & Sons).

It is *The Committee*'s recommendation to formally set up a Polish and a Hungarian National Group under our new constitution. It is to this end, that the above information has been prepared. With this newsletter you will find, in accordance with the requirements of the Constitution the necessary voting slips, asking the question:

"Are you in favour of the establishment of a ..... National Group" - YES / NO,

the "....." being replaced on the green slip with "Polish" and on the blue slip with "Hungarian". When you have made your choice, you should insert the voting slips in the anonymous white envelope which in turn should be placed inside the envelope already addressed to the ISCB Permanent Office in Copenhagen - and do not forget to enter your name, address and signature in the space provided on the back.

1996 Conference Accounts

ISCB 17 - Budapest 96

To: ISCB Secretary:
From: KOPA Auditors, Accountants and Tax Consultants, Budapest,
Date: 15 December 1996

Dear Mr Day,

I was requested to audit the financial settlement of the Conference held in Budapest in August 1996, by Dr Béla Hajtman, President of the Local Organising Committee of the Conference, on behalf of the International Society for Biostatistics.

On 2-4 December 1996, I reviewed the financial settlements of COOPCONGRESS Congress Organising Agency responsible for the technical implementation, where I was assisted by Emilia Korbuly, Conference Manager, and Eulalia Olah, Account Manager, on account of which let me express my gratitude once again.

Major auditing criteria were the following:

completeness of data
correctness of data and calculations
compliance of expenditure with ISCB objectives.

In the meantime, COOPCONGRESS Agency completed the financial settlement of the Congress. On 4 December 1996, it transferred into the ISCB account membership fees paid by those who attended the Conference. Due to technical particularities of banking procedures, the profits of the Conference will be transferred in January 1997.

I reviewed the financial settlement of the Conference by way of checking item by item some 95% of all invoices.

The audit has found that
- *the settlement included all revenues without fail;*
- *expenses were paid on the basis of the appropriate invoices;*
- *the financial settlement was arithmetically correct; and*
- *expenses were fully in compliance with ISCB objectives.*

In view of the above, I recommend that the financial settlement be approved.

Mrs Adrienne Tamasi, Certified Auditor

ISCB Society Accounts 1996

from Karsten Schmidt

ISCB ACCOUNTS, 31 DECEMBER 1996

	Danish account		UK accounts	Total
	DKK	£	£	£
Income				
Membership fees	45,774.21	4,554.65	4,827.50	9,382.15
Statistics in Medicine	128,274.70	12,763.65	14,850.00	27,613.65
Advertising, flyers	1,863.31	185.40	460.00	645.40
Earned interest	47,757.60	4,752.00	1,004.56	5,756.56
ISCB-17 surplus	156,425.00	15,564.68	0.00	15,564.68
	380,094.82	**37,820.38**	**21,142.06**	**58,962.44**
Expenditure				
Office supplies, photocopies	1,389.03	138.21	0.00	138.21
Postage, freight, fax, telephone	34,537.57	3,436.57	0.00	3,436.57
Bank charges	2,472.54	246.02	653.82	899.84
John Wiley	0.00	0.00	28,943.39	28,943.39
Travel expenses	25,725.04	2,559.71	0.00	2,559.71
Printing	37,269.38	3,708.40	0.00	3,708.40
Donations	0.00	0.00	0.00	0.00
Subscriptions	0.00	0.00	164.75	164.75
Adjustment of foreign currency	-0.24	-0.02	0.00	-0.02
Closing adj. of foreign currency	0.00	16,632.15	0.00	16,632.15
Administration	35,648.13	3,547.08	0.00	3,547.08
Temporary staff	6,967.50	693.28	0.00	693.28
	144,008.95	**30,961.40**	**29,761.96**	**60,723.36**
NET PROFIT:	**236,085.87**	**6,858.98**	**-8,619.90**	**-1,760.92**
Assets				
Current account, Barclays	0.00	0.00	804.49	804.49
High interest account, Barclays	0.00	0.00	23,853.54	23,853.54
Unibank, Denmark	187,426.77	18,649.43	0.00	18,649.43
Bonds, Danish State 5% 2004	683,419.20	68,001.91	0.00	68,001.91
	870,845.97	**86,651.34**	**24,658.03**	**111,309.37**
Debtors	12,324.60	1,226.33	400.00	1,626.33
Surplus, ISCB-16	22,794.62	2,268.12	0.00	2,268.12
Surplus, ISCB-17	156,425.00	15,564.68	0.00	15,564.68
Seed money, ISCB-18	132,041.25	13,138.43	0.00	13,138.43
Office equipment	18,003.05	1,791.35	0.00	1,791.35
	1,212,434.49	**120,640.25**	**25,058.03**	**145,698.28**
Liabilities				
Accrued expenses	69,502.58	6,915.68	0.00	6,915.68
Rebill acc. & acc. payable	282.26	28.09	451.86	479.95
	69,784.84	**6,943.77**	**451.86**	**7,395.63**
EQUITY CAPITAL:	**1,142,649.65**	**113,696.48**	**24,606.17**	**138,302.65**

(Rate of exchange DKK/£, 1996.12.31: 10.05. 1997.02.25/RS)

Book Review by Simon Day, UK (part 2)

Curtis L Meinert: Clinical Trials Dictionary—Terminology and Usage Recommendations

The Johns Hopkins Center for Clinical Trials, Baltimore.

In the last issue of ISCB News, Simon Day reviewed the above title and commented on the liberal scattering of little quotations ("some highly perceptive, some flippant, some just weird"). According to Curt Meinert, they are "everyday utterances of farmer friends and neighbors". We reproduce them below. We trust Dr Meinert's farmer friends and neighbours will forgive our flippant responses. Other publishable responses should be sent to David Warne; other non-publishable responses should be sent to Simon Day.

The safest treatment is the placebo

and fortunately many pharmaceutical companies are very good at producing them (or even developing drugs with wonderful safety profiles that are even less effective than placebo...)

The way to be sure is not to check

so three cheers (sorry, one cheer) for doing away with double data entry

All trials are collaborative, only some are multicentered

sadly, many of the multicentered ones seem to be non-collaborative

Collect no more than 10 times the data needed to answer the question of interest

and analyse each endpoint no more than 10 different ways

The way to cure a disease is to start a trial

and monitor it, clean and close the database, do the listings, analyses, report, and do some more trials, repeat above steps, and submit the dossier to numerous countries and...

Definitive is a label affixed 30 years after the fact

by which time it's too late to take the glory (but not too late to make money)

The difference between a good and a bad paper is 15 iterations

the good paper is usually the 2nd iteration and things go downhill after that

Save a nickel; spend a dollar

we don't understand (how many ECUs is that ?)

Only those who understand are informed

we don't understand that either (don't trialists fill in/out Informed Consent Forms ?)

Put too many pigs under a blanket and they all get away

and that we really, really don't understand! Anyway, how does he know!? (something about portfolio management perhaps ?)

Criticism is easier than craftsmanship
we disagree

Being a meta-analyst is easier than being a trialist
and reviewing meta-analyses is presumably even easier

In things lost, two moves equals one fire
or one computer upgrade

You can't get anything done if you don't have anything to do
yes, we're up to date with all our deadlines too

Leave too soon and you'll be late arriving
this sounds like one of those cheap holiday deals

You can't roller skate in a buffalo herd
this is so obvious that it deserves no comment (perhaps needs updating to inline skate)

For the actual number of people to be enrolled into a trial, divide the number promised by 4 and multiply the time stated for getting them by 2
note that this rule is recursive

Data and wine should be aged
sadly, not the wine we can afford

Common sense isn't so common
everybody knows that!

Start a trial and all the patients disappear
start a manuscript and all our good ideas disappear

The race is not always to the swift
this sounds like an e-mail (or a diskette, Simon) to the News Editor shortly before a publication deadline

When it comes to ideas: What's yours is yours and mine and what's mine is mine
true, but we thought of that first

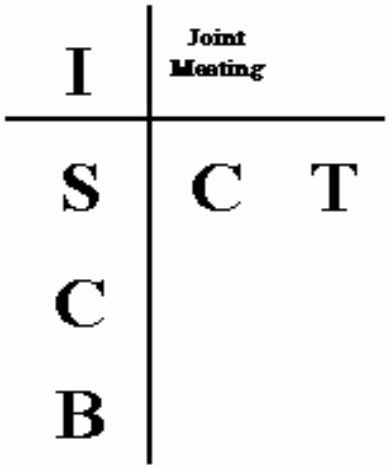
When you are up to your rear end in alligators, it's hard to remember you started out to drain the swamp
No comment, OK!? Just no comment!

1997 Conference: Update and Ramblings about Boston

from Nancy Geller

I saw the final version of the Preliminary Program Announcement for the 1997 Joint meeting when it came in the mail today. Although I had seen all of the pages previously, I had not seen the final format. (It would be foolish to admit I was one of the proof readers, wouldn't it?) I was a little bit surprised that I had to rotate it this way and that to try to read it, but once I "got the gist" I thought the reading was pretty engaging. The program looks really interesting and I hope that being a member of the LOC doesn't preclude me from spending most of my time at sessions.

So, at last, we are set for the Boston meeting. I have had some e-mail after the abstracts were reviewed and some submissions were rejected. I thought I'd begin by explaining how choices were made for abstracts to be presented as talks and as posters.



There were 318 submissions. The program committees of the two societies were joint for the purpose of evaluating contributed papers. The papers were divided according to the category the author selected and sent to three or four readers. (The program committee chairs selected the readers for each area.) Each reader evaluated her/his pile of abstracts on a scale of 1 (best) to 5 (worst) and the results were averaged. At a meeting in Baltimore (to which all program committee members were invited, but relatively few attended), it was calculated that we could have only 100 presentations. As you know now, there will be 5 simultaneous sessions most of the time and there are many invited sessions. Since the meeting was in Baltimore and Laurence Freedman was not in the USA, I represented the ISCB program committee. Two others who were present were members of both ISCB and SCT. There were four others who were from SCT. Two of these SCT people dealt only with the topics of data management, which had many submissions and ended up with one contributed paper session. At no time did I feel there was any preference given to SCT abstracts over ISCB. (There was no way to distinguish unless you knew which organization the person belonged to by his name.)

The abstracts were resorted into areas of similar subject matter (e.g. survival analysis; results of clinical trials; data management) for the organization of the oral and poster sessions. Generally it was the papers which got the highest rank which ended up being selected for oral presentation. There were certain exceptions to this, e.g. author preference for a poster session or those working on a certain session considering that a certain group of papers made a better fit. We ended up with 100 oral presentations and 130 posters. I hope most of you were satisfied with the decisions.

To get on to less serious matters, I wanted to mention a few things about Boston which you can find on the World Wide Web. If you look at the SCT home page, you will find a link to a Boston home page (http://www.bweb.com/), which is pretty good. One of the links from there is to the Zagat Guide, which is the US version (i.e. less expensive and less prestigious) of the Michelin Red Guide. I also found
http://www.city.net/countries/united_states/massachusetts/boston/
and
http://www.boston.com/home.htm
from which you can even read the Boston Globe. You can also download maps
(e.g. http://www.ndl.net/mamaps.html),
including the MTA (the "T" is the Boston version of the Tube) and a runner's map along the Charles River for those so inclined. These will give you a good flavour of the city we are about to visit.

I will close by mentioning that in Boston, the American accent takes on a new flavor, which is somewhat surprising for those who hear it for the first time. Bostonians use a very flat-sounding "a" which sounds like "ah". A true Bostonian will say, "Pahk the cahr at Hahvahd Yahd" for "Park the car at Harvard Yard." If you meet a native and you ask him (her) to say that sentence, (s)he will laugh because it is well known that those who ask just wish to laugh at the accent.

I hope to see you in Boston 6-10 July!

Book Review by Weichung Joe Shih, USA

Drug Stability - Principles and Practices
by Jens T. Carstensen
1995. 2nd edition, Marcel Dekker, Inc. New York

This is the second edition of the book; the first edition was published in 1991. Much new material, including both the scientific and the regulatory areas, has been added in the new edition. The book is written primarily for the drug stability scientist. Statisticians who are working with stability scientists in the drug development field will find this book useful in understanding both the subject matter and the current regulatory requirements for drug stability, but may find the statistical methods used in stability design and analysis inadequate.

The book opens with an overview of historical background, definitions and a glossary of pharmaceutical stability. In the overview sections and also in the last Chapters 16 and 17, the book provides vast information, as well as the author's comments, on the regulatory requirements on drug stability, especially the 1993 ICH (International Conference on Harmonization) and the 1987 FDA Guidelines. Since the pharmaceutical industry is generally a highly regulated industry by governments, the inclusion of this regulatory information and discussion is understandably very helpful for scientists working in the pharmaceutical industry. For academic pharmaceutical scientists, whom the author also considered as readers, this material on regulations may not be as interesting. In the meantime, it is also important to keep the scientific content in good order so that one can fully appreciate the different opinions and revisions of the regulations. In this regard, the author has done a good job in arranging and balancing the material properly in the beginning and then at the end of the book. As a text for academic courses as also suggested by the author, however, this book needs to give additional exercise problems for students.

The rest of the book covers solution kinetics (Chapter 2), kinetic pH profiles (Chapter 3) oxidation in solution (Chapter 4), catalysis, complexation and photolysis (Chapter 5), stability of peptides and proteins (Chapter 6), disperse and aggregated systems (Chapter 7), physical characteristics of solids (Chapter 8), solid state stability (Chapter 9), interactions of moisture with solids (Chapter 10), statistical aspects (Chapter 11), preformulation (Chapter 12), packaging (Chapter 13), physical testing (Chapter 14), modus operandi for a stability program (Chapter 15). As shown, the book is heavy on the side of stability science and regulation, as the book title suggested, and light on the side stability experimental design and data analysis, as many ISCB readers might desire. For the majority of ISCB readers who intend to be a statistical colleague of drug stability scientists, I recommend another book by the same publisher as an option: Statistical Design and Analysis in Pharmaceutical Science (Shein-Chung Chow and Jen-pei Liu, 1995).

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: 3 months after receipt).

Lutz EW (ed.)	Future demographic trends in Europe and North America: What can we assume today ?
Berry DA & Strangl DK	Bayesian statistics
Sprent P	Applied nonparametric statistical methods
Manly BFJ	Multivariate statistical methods: a primer
Wang C	Sense and nonsense of statistical inference

(2) Reviews awaited:

Anna Bartkowiak	Kocherlakota S&C (Marcel Dekker)	Bivariate discrete distributions
Aurelio Tobias	Scheaffer (PWS-Kent)	Introduction to probability and its applications
	Armitage P & Berry G (Blackwell)	Statistical Methods in Medical Research. 3rd edition.
Simon Day	Yandell BS (Chapman & Hall)	Practical data analysis for designed experiments

(3) Reviews long 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 him to pass on the books to someone who will review them !)

Software

(4) Reviews long awaited:

Stephan Evans	N, Nsurv, TESTIMATE	IDV, Gauting
Joan Houghton	Random	Wiedey
	Rancode	IDV

(If anyone knows these people, please ask them to pass on the software to someone who will review them !)

Publishers: I would be very grateful if you would send some new books *to the Society's Permanent Office* !

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ISCB News: News !

ISCB Changes of Address

Please inform the Permanent Office which looks after money and also the membership and mailing list databases.

ISCB: The Future

Boston, USA, 1997 and Dundee, Scotland-UK, 1998: please note announcement in this News. Further details to follow in 1997 and 1998 on

ISCB 20 - Heidelberg 99 ISCB 21 - Trento 2000

2001+: Proposals for conferences for these years are continuing to take shape, with various ideas, including Finland, under consideration. 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 SEDREG SubCommittee: Status of position paper:

1. The SEDREG paper on Statistics in European Regulatory Agencies has been sent to the Drug Information Journal.
2. Copies of the paper are sent to the regulatory authorities contacted for the survey.
3. A poster for the SCT/ISCB meeting in Boston.
4. The survey will be made available on the ISCB web site.

Book Review by Anna Bartkowiak, Poland

Multivariate Dependencies - Models, analysis and interpretation.

by D.R. Cox and Nanny Wermuth

Chapman & Hall, 1996, XII+255 pp. Series: Monographs on Statistics and Applied Probability, number 67.

The book is written for people with a moderate statistical background. The reader may gain a broader scope on some of the topics in the context of contemporary data analysis. The book does not replace manuals on the specific topics - it presents rather the ideas with emphasis on applications and interpretation of the results. Broadly speaking, the approach is by regression models with emphasis on visualisation of the interdependencies between the considered variables by directed or partially directed graphs using the principles of graph theory. Building an adequate model and proper interpretation of the results obtained from the analysis are thought to be of great importance and many hints and examples are given to show how this may be done efficiently.

Although the authors rely heavily on observational studies in the social sciences, they refer also many times to situations arising in clinical practice (e.g. effectiveness of treatments), therefore the book is of great value also for clinical practicioners. The language is very clear and without much mathematical burden, thus the matter presented can be understood by people less familiar with mathematical methodology and its tools.

The book has 8 chapters, an appendix containing a real data set (raw data on glucose control), references to 132 papers or books (one reference cited in the text, namely Cox 1994, is missing), lists of figures and tables, and author and subject indices.

In the "Introduction" we find some explanation about the scope of the topics presented in the book. The explanations are illustrated by situations arising in randomised clinical trials or prospective studies. The response (also called dependent or explained) variables may be continuous, nominal or binary, similarly the explanatory variables. It is advisable to distinguish among the explanatory variables: the treatment variables, the intrinsic variables representing properties of the 'individuals' in question, also the non-specific variables (e.g. describing broad groupings of individuals into blocks, centres, countries, etc.). The authors also present in this chapter some considerations on the nature and criteria for model selection and development.

Chapter 2 entitled "Aspects of interpretation" sets in more detail some tools to be used later for presenting the interdependencies among the variables. The principal tool here is a graph drawn on the basis of nodes-variables put in some boxes, depending on the nature of the variables. The interdependencies between variables are then symbolised by directed edges of the graphs. An (directed) edge between two variables symbolise that they are dependent, absence of an edge may mean a marginal or conditional independence. The presented practical examples advise the use of graph theory quite convincingly. A special subsection is devoted to interpretation of regression coefficients. Usually it is said that the regression coefficient - e.g. b_1, explaining the dependence of Y on X_1 in the regression Y=b_0 + b_1 X_1 + ... +b_q X_q + e - gives the change in E(Y) (the expected value of the variable Y) for a hypothetical unit increase in X_1, when the increase of X_2, ... , X_q is held fixed. A weaker but closely related interpretation arises in the circumstance when we consider two subpopulations of individuals differing by one unit in X_1 and with unchanged values for the other explanatory variables - then b_1 is the difference of the means of the two subpopulations. If X_1 represents a treatment then b_1 appears to represent the average effect on the response of an intervention in the system. However, suppose that Y is log survival time to a cardiac event and X_1, X_2 are respectively diastolic and systolic blood pressure. Then the notion of a change in X_1 with X_2 held fixed is likely to be highly artificial. Special care is given to interpretation of the coefficients of regression for a derived variable, say X_3=X_1 * X_1, to examine the interaction between X_1 and X_2. The problem is shown directly on an example, and a special method for dealing such cases is presented. Some traps waiting for the inexperienced user dealing with regression methods are shown.

Chapter 3 "Theoretical considerations" recalls in a parsimonious way mathematical formulae connected with (conditional) covariances, linear least squares regression and partial correlations. The case of (multivariate) data including also binary, nominal and ordinal variables is dealt with, illustrated by some easily conceivable examples. Some knowledge of the elements of matrix calculus is needed here.

Chapter 4 "Statistical analysis" deals with estimation problems in regression models and is, apart from Chapter 3, the most formal part of the book. For example, we find here presented shortly, yet in a concise manner, such topics as the method of least squares, weighted and generalised least squares, multivariate linear models, estimation by maximal likelihood, properties of the estimates obtained by these methods, also nonlinear least squares, constrained multivariate regression, constrained log-linear regression, likelihood ratio tests and profile likelihood. A separate subsection "presentation of regression analysis" is included.

Book Review (continued)

Chapters 5 and 6 ("Special methods for joint responses" and "Some specific applications") start the truly applied part of the book. Four real complex data sets (glucose control, determinants of university drop-out, disturbances in child developments and treatment of chronic pain) are analysed in detail seeking the interdependencies between the variables dealt with, visualising the established interdependencies by graphs (including directed graphs) and interpreting in a special way the constructed regression models. Each example is a masterpiece of statistical analysis.

Chapter 7 is entitled "Some strategical aspects". The authors are in principle against automatically building the regression model, e.g. by an automatic forward or backward search. They advise to build up the regression model sequentially beginning by checking the quality of the data, drawing plots of marginal associations with the purpose of gaining qualitative insight into the relevant (conditional) dependencies, and finding the nature of the variables (intermediate, explanatory). The authors do not recommend uncritical use of the strategy to set to zero all parameters with insignificant estimates.

Chapter 8, "Some more specialistic topics", addresses the issue of derived, hidden or latent variables and the broad topics connected with linear structural models. The use of graphical representation by structured graphs (with various kinds of edges) is shown.

The text of the book is illustrated generously with figures, which - although small - fit surprisingly well into the text and every detail has an extremely good visibility. The captions under the figures explain perfectly the topics displayed in the plots.

Book Review by Julia Singer, Hungary

Version 4 (Health and Sickness) of Essentials of Statistical Methods
by TP Hutchinson
Rumsby Scientific Publishing, Adelaide, 1995

Hutchinson invites us to read a very pleasant, "memory-jogging", refreshing, basic book about data description, probability and statistical inference. The title of the previous version (Essentials of Statistical Methods, 41 pages) reflects how concise and brief this introductory course is.

Part I tells the reader what is really essential about data description: the principal measures of location, measures of variation, graphical presentation, detection of outliers. data transformation and correlation. There is an abundance of examples, both medical ones and those from everyday life, especially from road circulation, and of practical proposals, for instance how to detect mistakes in hand calculations and how to use computer packages, showing that these need as much thought as the former.

Part II clarifies some important definitions like probability, independence, distribution, the relationship between different distributions, cumulative distributions, etc. The use of different distribution tables is explained in detail. The author's attention is focused in students and their exam, and he teaches them which formulae are worth remembering and which not. A nice, funny advice for students: "If you get an answer that is supposed to be a probability nut is negative or greater than 1, YOU'VE MADE A MISTAKE. If this happens in an examination, and you are in such a rush that you do not have time to correct it, you should make a note that you know you have made a mistake - otherwise, the examiner will think you are a complete idiot."

Part III, which considers statistical inference, succeeds in showing the beauty of this exciting field of statistics in a few pages. Omitting "statistical niceties", it presents the Central Limit Theorem, hypothesis testing and estimation. It includes such rarely met details as the standard error of the standard deviation and that of the median. Without being exact, its formulae have such a friendly form like:

confidence interval	=	best estimate	±	some number	x	standard error of best estimate

Sample size calculations and the use of random number tables are shown. There is even space to show controversies about the choice between hypothesis testing and confidence intervals, to teach what is a good estimate, and the pitfalls of routinely used significance levels.

Finally the reader is given various exercises which help the understanding of the basic notions. The best one, which I can recommend not only for beginners, is the task of looking up the newly learned words in an ordinary dictionary and to think about the improvement of the definition found there. If we do this task thoroughly and meticulously for all basic statistical terms, the stuff of a new statistical handbook will be ready.

ISCB Membership Information

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, Prevention Trials, Innovative Methods in Drug Development, Vaccine Trials, and Healthcare Assessment and Pharmaco-Economics.

Previous meetings in recent years have been held in Cardiff (1986), Gothenburg (1987), Innsbruck (1988), Maastricht (1989), Nimes (1990), Brussels (1991), Copenhagen (1992), Cambridge (1993), Basel (1994), Barcelona (1995) and recently in Budapest (1996).

A selection of talks at the meetings, for which papers are submitted for review and which are eventually accepted, 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, Cross-over Trials in Clinical Research, Analysis of Repeated Measures, Survival Analysis, Extending the Cox Model, and Statistical Methods for Genetic Epidemiology.

The current composition of the **Executive Committee** (ExCom) is as follows: **Officers:** President, Dr Karsten Schmidt (Denmark), Vice-President, Dr Nancy Geller (USA), Secretary, Mr Simon Day (UK), Treasurer, Dr Bernhard Huitfeldt (Sweden), and **Members:** Newsletter Editor, Dr David Warne (Switzerland), Past President, Dr Marc Buyse (Belgium), and Dr Mike Campbell (UK), Dr Bruno Cesana (I), Dr Albert Cobos (Spain), Prof. Ted Colton (USA), Prof. Michael Schemper (Austria), Dr Jørgen Seldrup (UK), and Prof. John Whitehead (UK).

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 ISCB also has 4 special **subcommittees** dealing with particular aspects of biostatistics. A particular focus in recent years has been statistics in drug regulatory affairs. The terms of references and function for the **SEDREG** SubCommittee is to finalise as soon as possible the position paper being prepared by the former Executive Team members. A final edition of the paper approved by the Committee must be available before the end of 1996 at which time the SubCommittee should be disabled. The chairman of the ISCB SubCommittee on Statistics in European Drug Regulation (**SEDREG**) is Prof. Wolfgang Köpcke, University of Münster, Germany.

The 3 other new subcommittees are on: **Fraud**: The SubCommittee will have the following goals: 1. to investigate the role of biostatistics in the prevention and detection of fraud in clinical research, and 2. to promote the role of appropriate biostatistical contributions in the assessment of misconduct The SubCommittee will produce a position paper reflecting the opinions of its members. The chairman is Dr Marc Buyse (Belgium).

Statistics in Regulatory Affairs: this SubCommittee will consider and influence the development of regulatory requirements, guidelines and other documents concerning the scientific aspects of data collection, management, analysis, and reporting. Also the SubCommittee will work on issuing new guidelines on these topics, where it is needed. The SubCommittee is chaired by Prof. Helmut Schäfer of Institute of Medical Biometry, Marburg (Germany).

Education: The SubCommittee will assess the feasibility of organising a one or two day course on contemporary methods in Clinical Biostatistics which will involve several members as lecturers and be presented in locations represented by the Society. This includes assessment of costs and organisation of such a course. Once feasibility is assessed, this sub-committee will be responsible for planning the course curriculum and selecting lecturers. The financial role of ISCB should be considered. The sub-committee will also receive requests from members that this course be given at their location and evaluate them. The first site at which the course will be presented is Barcelona, Spain from 25-27 June 1997 on the topic "Design and Analysis of Cross-over Clinical Trials" by Stephen Senn. Chairman: Mike Campbell (UK).

The Society publishes a **newsletter** thrice 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 to:

100557.2260@compuserve.com).

http:/ourworld.compuserve.com/homepages/David_W_Warne

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, Denmark.

Tel: +45 48 484 100, Fax: +45 48 484 200,

email: Iscb@post3.tele.dk

INTERNATIONAL SOCIETY FOR CLINICAL BIOSTATISTICS
1997
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ISCB Permanent Office,
P.O. Box 25,
DK-3480 Fredensborg,
Denmark,
Tel: +45 48 484100,
Fax: +45 48 484200.

Calendar

19-21 May 1997 — **Indiana, USA**

20th Annual Midwest Biopharmaceutical Statistics Workshop
Info: M. Ames, H3-M2516, Hoechst Marion Roussel, PO Box 9627, Kansas City, MO 64134-0627, USA
Tel: +1 816 966 5303, fax: +1 816 966 5778, email: mikames@hmri.com

25-27 June 1997 — **Barcelona, SPAIN**

1st ISCB short course on "**Design and Analysis of Cross-over Clinical Trials**" by Stephen Senn
Info: Albert Cobos, Novartis Farmacéutica SA, Gran Via de les Corts Catalanes 764, E-08013 Barcelona, Spain.
Tel: +34 3 306 4408, Fax: +34 3 265 1706, email: alberto.cobos@Pharma.Novartis.com

6-10 July 1997 — **Boston, USA**

ISCB18 (Joint meeting with Society for Clinical Trials)
Info: Mary Burke, Joint Meeting ISCB/SCT, 600 Wyndhurst Ave., Suite 112, Baltimore, MD 21210 USA
Tel: +1 410 433 4722, Fax: +1 410 435 8631,
email: sctbalt@aol.com, WWW: http://members.aol.com/sctbalt.

22-25 July 1997 — **Leicester, ENGLAND-UK**

Burning Issues in Medical Statistics
Info: B. Teather, Exec. Secretary BIMS Conference, Dep't of Medical Statistics, De Montfort University,
Leicester LE1 9BH, England-UK
Fax: +44 116 250 6114, email: bte@dmu.ac.uk

8-12 September 1997 — **Fredericton, NB, CANADA**

Annual Meeting of the Statistical Society of Canada
Info: R.A. Mureika, Dep't of Mathematics and Statistics, The University of New Brunswick,
PO Box 4400, Fredericton, NB, E3B 5A3, Canada
email: mureika@math.unb.ca

15-16 September 1997 — **Paris, FRANCE**

ASU Biopharmacie '97: Statistical Methods in Biopharmacy, 3rd International Meeting.
Info: B. Scherrer, Institute de Recherche Jouveinal, 3-9 Rue de la Loge, F-94265 Fresnes Cedex, France
Fax: +33 1 40967691

1-4 December 1997 — **Adelaide, SA, AUSTRALIA**

Biometrics 97 - biennial meeting of the Australasian region of the International Biometrics Society
Info: A. Verbyla, Biometrics 97, Dep't of Statistics, University of Adelaide, SA 5005, Australia.
Tel: +61 8 8303 3218, fax: +61 8 8303 3969, email: biom97@maths.adelaide.edu.au

24-28 August 1998 — **Dundee, SCOTLAND-UK**

ISCB19
Info: Andrew Lawson, University of Abertay Dundee, Statistics Division, School of Maths., Bell Street,
Dundee DD1 1HG, Scotland-UK
Tel: +44 1382 308604, Fax: +44 1382 308877, email: a.lawson@tay.ac.uk

Summers 1999 & 2000 — **Heidelberg, GERMANY & Trento, ITALY**

ISCB20 & ISCB21
Info: ISCB Permanent Office, PO Box 25, DK-3480 Fredensborg, Denmark.
Tel: +45 48 484 100, Fax: +45 48 484 200, email: Iscb@post3.tele.dk