Use and Misuse of Computers in the Design and Analysis of Dental Clinical Trials

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The use of computers in the 1980's for work or play has reached the level where the television ads assume that each of us needs, wants, and will buy a personal computer (PC) today for use either at home or the office. The constantly changing technology and proliferation of computers into every corner of our lives have occurred with such rapidity that it is no longer possible for even the most experienced computer users to keep abreast of technological changes in today's market.

Along with the computer changes come newer, more sophisticated programs that do everything you've ever thought of and still have time left to chat with you while generating volumes of information in a few seconds. How can dental researchers in the 1980's make the best use of modern electronic data processing to facilitate their research? In the area of clinical trials and epidemiology, it is not uncommon to collect, process, and analyze very large data bases. The efficient use of computers and computer programs can reduce the magnitude of this task to a reasonably manageable routine.

One of the most important considerations for clinical trials – one often receiving the least attention from clinicians – is the method used for collecting information in an accurate, useful manner. Various recording systems have been used over the last fifteen years, many of them complicated or tedious, and some tending to increase the volume of error or omissions in the data. Ethically, it is as indefensible to collect useless or unusable information from patients as it is to conduct a clinical trial which doesn't answer the question it purports to answer.

Today, most clinical investigators use some variation of a classification system of letters and numbers for designating the condition of each permanent or deciduous tooth or tooth surface, as indicated in Fig. 1. This type of system originated with Klein and Palmer in 1940 and is still used with various modifications today.[5] Klein also devised one of the first automated systems combining mark sensing with punched cards.[3] Manual recording and punched cards are still in use; however, these methods may add significant processing time and may generate a large error factor in data collection. One swifter and more efficient method, particularly for large clinical trials, is the use of optical mark readers (OMR). This method greatly reduces error created by hand tallies or keypunching.

Once the data from the examination record are stored on the computer files, editing can be accomplished by programs written to detect missing or illogical observations. Corrections can be made *via* interactive terminals, so that a complete edited data set is then ready for analysis. Statistical programs can be designed and used to do basic tabulations of information. If a large volume of records is involved, analysis can be facilitated by using large computers with access to standard statistical packages (so-called "canned routines").

Data tabulations usually include the means and variances (standard deviation, standard error of the mean) of the basic components of decayed, missing, or filled (DMF) surfaces or teeth. These can be obtained for any single tooth or combination of teeth or surface types. Distribution of the dependent variable DMF surfaces or teeth by age, sex, and initial DMFS may be included. Examination of these basic tabulations helps the examiner to determine if the information is logical and in proper order. User-written programs or statistical packages can then be applied to particular analyses of the data, depending on the design of a specific clinical trial and the hypothesis being tested.

EXAMINER CODES

Tooth	Status	Call
Deciduous	Caries Free	D
Permanent	Unerupted	U
"	Caries Free	S
"	Extracted (caries)	E
"	Extracted (no caries) or Excluded from population	Y

Surface	Carious	Filled
Occlusal	X	5
Lingual	0	6
Buccal	1	7
Mesial	2	8
Distal	3	9

Fig. 1 – Coding system for classifying tooth and surface status on caries examinations.

However, the efficiency of any system to produce accurate information is quite dependent on the data collection process. Examiners must be calibrated as accurately as possible in the use of criteria and coding for measuring the disease. The record sheet must be designed to be functional for the examiner, for the persons recording the information, and for the person or machine transferring the information into the computer. Forms for optical mark readers in the early 1970's had design limitations. As machines have become smaller and more flexible, the forms have become easier to organize to make them more usable by everyone. Only a few minutes are required to train field personnel to mark the form accurately. However, it is necessary to follow directions precisely, or errors will be created which increase the correction time. Well-trained recorders are an asset, since they will be able to check at the time of examination for missing data or illogical tooth patterns.

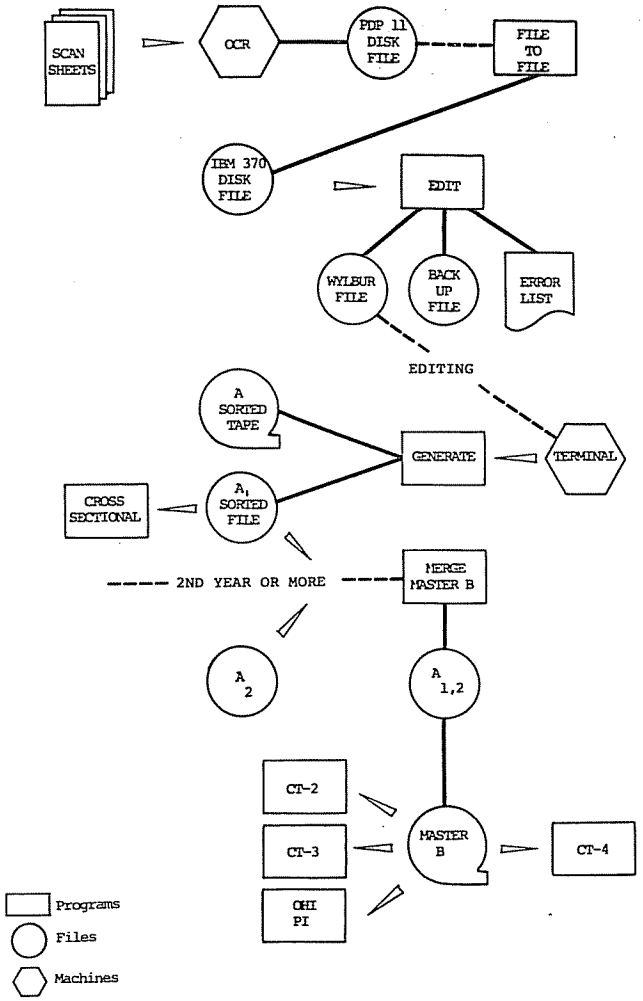

Fig. 2 – Flow chart of NIDR data processing system for caries clinical trials.

It has been suggested that a microprocessor can be used in the field at the time of the dental examination to enter data directly *via* a keyboard for storage on a magnetic disk.[1] This technique – using a forms image on the video monitor, with an editing program signaling for certain obvious errors, such as blanks or numbers out of range – is certainly a more direct way of entering information onto computer disks. This would be a successful mechanism for small studies on patients in a clinic, but I believe it has two possible drawbacks in large-scale clinical trials. First, it would definitely need a trained person to enter the information rapidly, understand the error messages, and know how to correct them. Thus, local people at a study site would need to be familiar with keyboard data entry procedures to be used as "recorders". Second, if anything happens to the storage device, there is no hard-copy back-up to revert to later. It would probably also take longer to examine each individual.

At NIDR, a system which is used to process and analyze a large number of clinical studies and epidemiological surveys within the same year has evolved over time. The flow chart of the current NIDR processing system for caries clinical trials is shown in Fig. 2. The current use of optical readers has progressed from the cumbersome punching of cards by mark sense machines, first suggested by Klein, to optical mark readers which transmit coded data directly from one- or two-sided documents to a computer disk or tape *via* direct transmission lines.

The record file is then available for editing, re-coding, and sorting of the measured variable into any order desired. The OMR machines are capable of some editing. Or, user-designed edits written in a higher-level language, such as Fortran or PL/1, can search for missing identification, such as case number, sex, age, or missing tooth or surface data. Corrections are made directly to the disk file by means of an interactive computer terminal. The records are sorted in some uniform manner, such as case number, age, or grade within treatment group, for further analysis. A safety precaution is the production of a copy of edited data stored on a separate disk file or tape for back-up in case of loss or scrambling of the original data base.

In the second or subsequent years of a clinical trial, the records from baseline and earlier years must be merged with the current records, creating a new master file containing all examinations for each person. To facilitate programing of longitudinal studies, missing records for individuals have a place-holder record, so that a uniform system of five records *per* individual is always constructed (Master B tape). Again, a back-up of master records is a wise addition.

Standard programs have been designed to do simple tabulations and cross-sectional or longitudinal analysis the same way on each clinical trial. This helps us evaluate the basic findings in light of previous experience. A cross-sectional program currently written in Fortran produces the basic tabulations listed earlier (Fig. 3.)

Other programs available for our use have been written by various users over the last ten years in several computer languages – Fortran, PL/1, Basic, and SAS. These programs can analyze change between any two exams for a dependent variable – usually DMFS, but sometimes others, such as DMFT or any sub-set, such as first molar decayed and filled occlusal surfaces – by any classifying variable, such as age, sex, initial DMFS, or treatment group.

X-S L.I. APF AND CLEANING PERMANENT DENTITION GROUP 1 PAGE 48 10/16/79

BOTH ALL SURFACES

AGE	N	ADJ N	MEAN DMF	ST DEV	% DMF	%O/DMF	%F/DMF	%M/DMF
ALL	484	484	4.083	4.279	4.59	25.61	71.61	2.78
10	78	78	3.103	3.282	4.24	31.82	68.18	0.00
11	226	226	3.646	3.569	4.37	27.06	70.51	2.43
12	170	170	4.988	5.063	4.93	23.11	73.94	2.95
13	10	10	6.200	7.554	5.02	16.13	67.74	16.13

Fig. 3 – Example of basic tabulations produced by standard cross-sectional program.

Transition Matrix - All Teeth Group 1

First Exam		Second Exam: Deciduous CF 1	CA 2	FI 3	UN 4	Permanent CF 5	CA 6	FI 7	DC 8	EO 9	Totals
CF	1	6	0	0	3	26	1	0	0	0	38
CA	2	0	2	1	1	4	1	0	0	0	9
FI	3	0	0	4	8	6	0	0	0	0	18
UN	4	0	0	0	4	19	2	4	0	1	30
CF	5	1	0	0	1	120	8	14	2	12	158
CA	6	0	1	0	0	2	1	10	1	0	15
FI	7	0	0	2	0	0	0	5	0	0	7
EC	8	0	0	0	0	1	0	0	1	0	2
EO	9	0	0	0	0	1	0	0	0	2	3
Totals		7	3	7	17	181	13	33	4	15	280

The Number of Children in the Group is 10

CF = Caries-Free CA = Carious
FI = Filled E = Extraction
EC = E for Caries EO = Other Reasons
UN = Unerupted

Fig. 4 – Example of transition matrix produced by standard longitudinal clinical trial program.

Transition matrices.

A useful mechanism in computer programs which can be used to construct increment or other changes in longitudinal studies is a transition matrix as illustrated in Fig. 4.[4] An individual's scores for each tooth or surface code can be accumulated for each year in a matrix defined by the caries status codes. Then, by adding and subtracting boxes, any quantity that an investigator is interested in – such as baseline DMFS, increment, net increment, or current status of an individual tooth or surface type – can readily be determined. In the example (Fig. 4), all tooth codes for a treatment group of ten individuals have been indexed into a matrix. Initial DMF for teeth would be determined by adding the totals for rows 6 (carious), 7 (filled), and 8 (extracted for caries) (answer = 24). Net increment totals would be calculated by adding teeth that went from caries-free at baseline – row 5 – to carious, filled, and missing at 2nd exam – columns 6, 7, and 8 (numbers within rectangle) – and subtracting the DMF teeth at baseline classified as caries-free on the second exam – rows 6, 7, and 8 of column 5 (numbers within oval). Many other questions can be answered from such a matrix. It is also possible to analyze small sub-sets of information – for example, only the status of first molar occlusal surfaces for 12-year-olds at two exams. The transition matrix in longitudinal trials is a dynamic tool.

Statistical computer packages.

Today, standard computer packages are available to the data analyst to perform a myriad of statistical procedures. Three of the most widely-used program sets are the Statistical Analysis System (SAS), Biomedical Computer Programs (BMD-P series), and the Statistical Package for the Social Sciences (SPSS-X series.) Each of these systems of statistical procedures was originally written for a specific audience of users and therefore varied greatly in its data handling techniques, output design, statistical explanations, and, especially, the directions for running the programs (user manuals). Although some of these packages were originally system-dependent, they are now available on almost any size computer system.

It is difficult to discuss the problems associated with computer packages. The most serious problems are not in the statistical packages themselves but in their use by persons lacking either experience or a good foundation in statistics. Most of the problems result from misuse of statistics rather than a misuse of computers or computer packages. The user, whether clinical investigator or statistician, needs to know what questions are being asked, the usual behavior of the types of data that are being analyzed, and the assumptions that can be made about them. He should also have a firm foundation in understanding the application of statistics to the data. Some statisticians are very concerned that the statistical packages are too easy to use and that they may be fostering a widespread misuse of statistics by making it easy to perform an inappropriate analysis. On the other hand, restricting access to sophisticated techniques is neither constructive nor realistic in the current computer-use market.

To aid the novice user of statistical computer packages, each product has documentation available, the most common being a user's guide or manual. During the last eight years, the American Statistical Association has tried to set up criteria for evaluating packages and their accompanying documentation. Invited papers and reviews have been published comparing the strong and weak points of such packages as SPSS and BMDP.[6] These discussions are very useful for understanding the scope of material available and the limitations of the documentation. It is particularly interesting to note the differences among the packages in their statistical discussions. Some are written at a very basic level; others assume a depth of statistical knowledge not necessarily possessed by the user. However, the packages are evolving all the time, and clearly reviews become obsolete almost before publication. On the other hand, the reviews and discussions of the statistical packages have caused the designers of the packages to make modifications to correct some of the deficiencies observed by the reviewers.

It is easier to run certain programs in one system than another. It would be most helpful to all users if there were some uniformity in the packages – in particular, a standard format for data definition. Then, a data set already stored on the computer files could more easily be used with the statistical programs of any package, without the need to spend an inordinate amount of time re-formatting the data to meet new specifications. It is also useful that, in a number of packages, such as BMDP and SAS, user-written programs and Fortran sub-routines can be accessed. SAS can also invoke BMDP sub-routines.

Specific programs that are very useful for design and analysis of dental clinical trials range from a simple program, which accesses a random number generator for assigning patients to treatment groups, to a General Linear Models Program, which allows for sophisticated multivariate analysis with missing cells or data.[8] Most of the analyses discussed at this meeting – such as confidence intervals, significance tests, interclass correlation, Kappa, Covariance[7], non-parametric tests for categorical data, simulation, life tables, and survival curves – can be accomplished most efficiently using available statistical packages.[2]

New statistical programs and specific variations of established programs are continually being added. Various errors in specific programs have been noted and usually corrected over time. The analyst will be more confident in the use of packaged programs, especially new ones, if

there is a good example or explanation given in the documentation. It is a sound practice to test programs using textbook examples (if available) or small amounts of data which can be checked mathematically by hand.

A further caution to the statistician working with investigators in clinical trials: Merely handing the clinician a computer print-out of results of the analysis – whether small or, worse, very large – is not very helpful. "What does it mean?" Being inundated with a number of result options, foreign terms and abbreviations, or masses of paper will often cause researcher mis-interpretation and poor description of the statistical analysis in oral or written presentations. Depending on the clinician's statistical background and experience in dental clinical trials, the statistician should describe both orally and in writing what methods he used and why, and the meaning of any output options he wishes to discuss with the researcher.

Overall, the computer, whether small or large, is an invaluable tool in the design and analysis of dental clinical trials. The availability of a wide variety of statistical programs has increased the options for more refined analysis of the data. Easier collection and editing of data *via* interactive terminals, optical marked forms, and on-line tape recorders or PC's have decreased the time between examination and analysis.

REFERENCES

1. GAMBLE, A. and MANDER, C.I.: Application of a Microprocessor for Collection of Dental Epidemiological Data, *Community Dent Oral Epidemiol* 9:300-301, 1981.
2. HEIBERGER, R.M.: The Specification of Experimental Designs to ANOVA Programs, *Amer Statistician* 35:98-104, 1981.
3. KLEIN, H. and KRAMER, M.: A Dental Examination Record Form for Statistical Machine Tabulation, *J Dent Res* 27:170-174, 1948.
4. MARTHALER, T.M.; BANDI, A.; and STEINER, M.: Computers in Preventive Dentistry, *Int Dent J* 30:201-213, 1980.
5. MOLLER, I.J. and POULSEN, S.: A Standardized System for Diagnosing, Recording and Analyzing Dental Caries Data. *Scand J Dent Res* 81:1-11, 1973.
6. A Review of the Manuals for BMDP and SPSS, Invited Papers, *J Amer Stat Assoc* 73:65-98, 1978.
7. SEARLE, S.R. and HUDSON, G.F.S.: Some Distinctive Features of Output from Statistical Computing Packages for Analysis of Covariance, *Biometrics* 38:737-745, 1982.
8. SPEED, F.M.; HOCKING, R.R.; and HOCKNEY, O.P.: Methods of Analysis of Linear Models with Unbalanced Data, *J Amer Stat Assoc* 73:105-112, 1978.

Use and Misuse of Computers in the Design and Analysis of Dental Clinical Trials: Discussion of Ms. Brunelle's Presentation

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I would first like to compliment Ms. Brunelle for a fine and thorough review of her topic. There are many "uses" for computers today in the clinical testing area, and a number of them have just been described by Ms. Brunelle. There will undoubtedly be more uses in the future. This is the easier part of this topic to discuss. The more difficult part of the topic to discuss is the "misuse" of the computer. I believe this could more accurately be re-defined, not as "the misuse of computers", but as "the misuse of statistics" which is facilitated by the use of computers.

First, I would like to mention some specific uses of computers which may not be so obvious to some. These uses do not involve statistical analyses but involve the use of the computer to help ensure double-blindness in studies and ways to take some of the time-consuming clerical work out of preparing for studies.

In the area of double-blindness, the computer can be used to generate random numbers with restrictions and allocate the numbers to specified treatment groups. For example, if 3000 subjects were to be recruited for three treatment groups, the numbers from 1 to 3000 could be allocated to groups with restrictions to 3's. In other words, the numbers 1, 2, and 3 would each be allocated to one of the treatment groups, with the same for the numbers 4, 5, and 6, and so forth. This random allocation can be stored in the computer for future reference, and the numbers themselves will become the subject identification numbers for the remainder of the study.

For assignment of subjects to treatment groups, the computer can be used to generate sheets of random permutations of the treatment groups with any number of factors, such as age, sex, DMFS scores, etc.

Using the stored master file of random allocation of numbers to treatment groups, the computer can be used to generate a file of tamper-proof, opaque, active disclosure envelopes. These envelopes are manufactured as three-part continuous computer forms and are similar to the W-2 forms with which we are all familiar. The computer then prints on them, showing the treatment identity for each subject. The first part is stripped away, leaving sealed envelopes that are tamper-proof. As subjects are randomly assigned to treatment groups, the subjects' names are then written on the envelope containing the subject number which has been randomly assigned. These envelopes are retained by the investigator for his use during the study in the event of an emergency, rather than having a master list with all the subjects' treatment identities.

As assignment progresses, rosters can be created with each subject's assigned number, name, and location (school, classroom). This roster can be entered into the computer and can be used to generate product labels that bear each subject's name and number, to make each subject unique and avoid the use of group codings which could accidentally be identified. These labels can be printed by the computer in any order, such as by school by classroom, to facilitate distribution of products to subjects by the investigator's staff.

A very time-consuming part of the investigator's preparations for field work is in getting forms ready to be used. The master roster stored in the computer can be used to pre-print continuous examination forms with the necessary subject identification information. Again, the computer can sort and print these forms in any order requested.

I would like at this point to speak a few minutes on