Eur J Clin Pharmacol (1994) 46: 389–391

European Journal of Clinical Pharmacology


*Conference report*

# Population approaches in drug development*

## Report on an expert meeting to discuss population pharmacokinetic/pharmacodynamic software

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Received: 15 December 1993/Accepted in revised form: 24 February 1994

**Abstract.** An expert meeting to discuss population pharmacokinetic/pharmacodynamic software was held in Brussels in November 1993 under the auspices of the European Co-operation in Science and Technology (COST), Medicine (B1) programme.

Recently developed statistical methods offer the possibility of gaining integrated information on pharmacokinetics and response from relatively sparse observational data obtained directly in patients who are being treated with the drug under development. These methods can minimize the need to exclude patient groups and also allow analysis of a variety of unbalanced designs that frequently arise in the evaluation of the relationships between dose or concentration on the one hand and efficacy or safety on the other relationships that do not readily lend themselves to other forms of statistical analysis.

The purpose of the Brussels meeting was to evaluate the state of both existing software and software under development, and to specify the needs and wishes of potential users of such software. It was apparent from the meeting that software development for population data analysis is currently a very active area of investigation and that several very good packages are already available, with more in development.

The general consensus of the meeting was that well validated, easy to use software was essential to the implementation of the population approach to drug development.

**Key words:** Population approach, Drug development; software, pharmacokinetics, pharmacodynamics

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An expert meeting to discuss population pharmacokinetic/pharmacodynamic software was held in Brussels in November 1993, under the auspices of the European Co-operation in Science and Technology (COST), Medicine (B1) programme[1]. The meeting developed from a conference (New Strategies in Drug Development and Clinical Evaluation: the Population Approach) held in Manchester in September 1991 [1], also organized under the auspices of the COST B1 program. The population approach, using recently developed statistical methods, offers the possibility of gaining integrated information on pharmacokinetics and response from relatively sparse observational data obtained directly in patients who are being treated with the drug under development. The methods allow the incorporation of data from patient groups which are often excluded and also the analysis of a variety of unbalanced designs that frequently arise in the evaluation of the relationships between dose or concentration on the one hand and efficacy or safety on the other relationships, which do not readily lend themselves to other forms of statistical analysis.

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The methods and programs that were discussed included four different implementations of maximum likeli-

[1] The participants are listed on title page

hood (the NONMEM program [2], the EM (expectation-maximization) algorithm [3], nonparametric maximum likelihood [4], nonparametric EM [5]) as well as a full Bayesian approach [6]. Discussion concentrated on the following topics: data input, graphical data exploration for diagnostics and model building, algorithms and their implementation, model implementation, output, and support and documentation. We report here the consensus of the meeting relating to these topics.

## Data input

It was agreed that a data input system should be both integrated (i.e. data directly available without manual transfer procedures) and interactive (i.e. all data available at any time). The database system may be part of the population software, or data should be readily importable from one or several dedicated data management softwares. The latter possibility is of particular concern for a pharmaceutical company that relies on a particular laboratory information system (LIMS). In any case, data protection and an audit trail should be implemented in the database.

NONMEM is currently the most widely-used population software package, with its pre-processor NMTRAN. The structure of the required ASCII data file is governed by the time elapsed since the start of treatment (or date and clock time). This structure is well suited for many applications, including pharmacokinetics. It is driven by the notion of an event, which can be either a dosing event (drug administration) or a sampling event (blood concentration). Each event is associated with one record. Although the meeting did not recommend NONMEM/NMTRAN as a standard, software developers would be well advised to ensure at least compatibility of their input file with this reference, or to provide an interface to it.

Internal consistency of the database should be ensured as far as data format is concerned (e.g. dichotomous versus continuous variables, dates, times). The possibility of dealing with missing values, of recoding variables, and of sorting and selecting subgroups of cases should also be available. Data entry should be sufficiently flexible to deal with complex dosing histories. At the present stage it was not felt useful to define a standard database format.

## Graphical data exploration for diagnostics and model building

It was generally agreed that visual inspection of graphs before, during, and after data analysis is a crucial issue in population analysis. Graphical modules may be integrated with or interfaced to the population software. When they are part of the population software, graphical techniques are more readily available and become part of the model building phase (eg residual plots). If an interface to a dedicated graphical software package is provided, the ease of data transfer is of particular concern. In addition, it was felt important that the population software should be upgraded simultaneously with changes in any associated statistical-graphical package.

## Algorithms and their implementation

The meeting agreed that the availability of different methods of population analysis in software packages or within the same package is to be considered as an advantage, since each method has its own features, allowing further research on strategies for data analysis.

Thanks to an initiative of the American Statistical Association, a comparison of various population approaches and of the different methods that underlie them was carried out in 1992, through the analysis of a data set (136 patients, 361 serum concentration measurements) for quinidine. The methods used to analyze the data were NONMEM, Gibbs sampling, semiparametric maximum likelihood, and nonparametric maximum likelihood. The main result was that the different methods gave close results with respect to clinical relevant co-variates, and differed only in marginal details. In all cases the reported computing times were of the order of several hours of CPU time for one run on workstation equipment.

Clearly, the opportunity to apply several methods to a given data set is one means of validating an analysis: it strengthens confidence if the results are consistent; it highlights problems if discrepancies are observed.

The group felt that full details of the algorithm and its implementation should be available to the user and that such information was felt to be crucial for adequate data analysis and evaluation of results. The extent to which information on the methodology should be published and peer-reviewed was discussed, but no specific conclusions were reached.

The availability to potential users of well documented study cases was felt to be an important issue. It would be interesting to have access to simulated and real data sets that could be used for software development and evaluation and for training purposes. The idea here is to evaluate the software and not the user, and so the "best" model and parameter estimates should be known. The COST B1 steering committee on the population approach to drug development will actively promote an initiative, together with other groups or institutions, to produce data sets that can be used for software evaluation and user training.

Numerical stability was also discussed, and it was concluded that software packages should have good error recovery and informative diagnostics.

## Model implementation

Population approaches adapted to sparse data situations tend to use structural models of lesser complexity than "data-rich" situations. Nevertheless, a minimum library should contain at least the possibility of bolus, first-order, and zero-order input functions and up to three disposition exponentials for pharmacokinetic models. Minimal pharmacodynamic requirements include the linear, log-linear, and sigmoidal $E_{max}$ model. In addition, a pharmacokinetic-pharmacodynamic link model should be provided. It is highly desirable that users should be able to implement their own models in a user-friendly fashion. It should

be possible to define both algebraic (ie closed form) and differential equations.

In population analysis using sparse data, the quality and reliability of the results depend on the level of expertise of the data analyst to a greater extent than is the rule for other more classical statistical approaches. The software should therefore contain the possibility of evaluating the model and its predictive performance, either with a given study data set or with a separate data set (test sample).

## Output

Graphical issues have been discussed under graphical data exploration. Output of parameters and results in tabular format is also essential. The software should be capable of formatting the output in a style dictated by the user, or the output should be readily transferable to other software. In addition, population software intended for use during drug development should contain a log file of 'actions taken'. Such a file could also serve as an audit trail. The exact nature and extent of the information that should be available in the log file was not discussed.

## Support and documentation

Continuing support is vital. Software developers should update their software in line with modifications in hardware and complementary software, particularly if that software (e.g. graphical packages) is part of the working environment.

As for any software, there should be complete and adequate documentation, which should be structured logically, properly indexed, and cross-referenced. This is a must for wide acceptance of the software. On-line help was thought to be desirable. Electronic mail may provide an additional service, either for informal exchange between users or for dissemination of information by the developer.

Good tutorials are useful but cannot replace training courses. Tutorials can be electronically supported or part of the printed documentation. Training courses organized by the developers were considered to be important. These courses should be directed towards the use of the software. They should not, however, be substitutes for more elaborate education in methodological issues, which should be promoted in parallel. Some concern was voiced that if the software was excessively user-friendly it could be abused. However, it was agreed that results would eventually be peer reviewed and that this was not a problem for the scientific community at large.

## Other issues

The group discussed several other issues relating to population analysis. In particular, the proper collection and management of data was seen to be crucial to successful data analysis. This is an area of much current concern in the pharmaceutical industry and is a very difficult task, especially in the context of clinical study logistics.

## Conclusions

The main message from the meeting was that the development of population software is an area of active interest. It was not the purpose of the meeting to compare existing software. There was general agreement that well validated, easy to use software was essential to the implementation of the population approach to drug development. The following is a summary of the important conclusions from the meeting.

- Software should be sufficiently user-friendly to allow an informed user to carry out population pharmacokinetic/pharmacodynamic analysis.
- It is essential to be able to fully specify sparse data, including data arising from complex dosing histories.
- It should be possible to specify pharmacokinetic and pharmacodynamic models in a completely flexible manner.
- Good graphical diagnostics are essential for population analysis.
- It is crucial that software is adequately supported and maintained.

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