GOOD BIOMETRICAL PRACTICE IN MEDICAL RESEARCH

Guidelines and Recommendations

Ulrich Mansmann[1], Katrin Jensen[1], Peter Dirschedl[2]

[1] Institut für Medizinische Biometrie und Informatik, Universität Heidelberg, INF 305, 69120 Heidelberg
[2] Institut für Med. Informationsverarbeitung, Biometrie und Epidemiologie, LMU München, Marchioninistr. 15, 81377 München

1 Preface

In December 1997, an international commission, established on behalf of the presidency of the 'Deutsche Forschungsgemeinschaft' (DFG), formulated the following task: "Scientific societies shall develop, for their areas of activity, standards for good scientific practice, oblige their members to adhere to these standards and make them public."

The *Medical Biometry* section of the 'German Association for Medical Informatics, Medical Biometry and Epidemiology' (GMDS e.V.) supposed the present statement on good biometrical practice in medical research. These guidelines summarise the scope of the tasks and responsibilities of a biometrician in medical research. It is primarily directed at members of the GMDS e.V. but is also relevant to all biometricians in medical research.

The main message of the statement is that biometricians in medical research not only have to abide by national and international legislation and guidelines (like AMG, MPG, GCP, ICH guidelines, CONSORT etc.), but also they have to contribute to sound methodological reasoning and to take responsibility and co-operate from the outset of a project.

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

2 Ethical Concerns

Scientific justification, autonomy of involved subjects, risk-benefit considerations, and scientific quality are crucial to the ethical value of a research project [2]. Victor identifies all four aspects as closely related to the field of biometry [3].

The biometrician is, therefore, clearly responsible for addressing ethical issues related to a medical research project. Important aspects of a medical research project are planning, reviewing, execution, monitoring, and dissemination of the results. In all these steps the biometrician contributes majorly to the *scientific quality* of the project.

In order to fulfil his/her responsibilities the biometrician has to actively participate in the research process. It will often be necessary to take active steps towards implementing and ensuring scientific quality within a project rather than waiting to be assigned the appropriate role.

Planning: The biometrician is crucial in collecting reliable information (e.g. from systematic reviews) to justify the relevance of the project, assessing the feasibility and operationalisation of its goals, developing a study design which prevents unnecessary harm to the subjects involved and lays the foundation for a successful project conduct, preparing the sections of the study protocol relevant to biostatistics.

Reviewing: The biometrician should be active in ethics committees or as reviewers of medical journals to secure and control scientific quality in medical research: *Statistical refereeing is a form of fire fighting* [4]. Furthermore, reviewing ongoing projects as external experts to safeguard patients' interests and taking part in the review of planned projects submitted for public funding. Co-operating as experts with regulatory bodies and courts involved in disputes over the efficacy of medical treatments. Co-operating as reviewers for medical journals.

Execution: The biometrician has to be active in assessing the quality of data collection, monitoring analytic procedures and information flow, intervening in the study process to ensure the necessary respect for basic ethical and methodological principles, performing the analysis. Adapting statistical methodology to changing study design characteristics.

Dissemination: Generally, the biometrician is a member of the group that writes up the project's final report. The biometrician is responsible for the appropriate presentation of the results (including appropriate tables and figures) and for the correct interpretation of the findings in the spirit of unbiased objectivity. This includes taking responsibility for publishing important findings of the research project. A special form of dissemination is statistical teaching; assisting medical researchers to understand published results [5] and the statistical principles behind research projects.

3 Biometricians role and contribution in shaping projects and the Project Development Plan

Medical research project should address an important medical problem and should be able to contribute in a relevant way to its answer. This requires collecting the appropriate information pertaining to the project proposal. A biometrician should participate in this process in order to ensure adherence to the principles of evidence based medicine, clinical epidemiology, and information retrieval and to ensure correct interpretation of relevant information [6]. It also requires knowledge of the respective disease specific guidelines issued by regulatory bodies and scientific medical associations.

This process results in accepted endpoints, relevant input for sample size considerations (effect size, variability, stratification), important insights into study logistics and experience from earlier research projects. These findings and conclusions should be documented in a project development plan which identifies the key decision points of the research project. An application for project funding typically requires a project development plan. Templates are available for the DFG and EU agency sponsored projects.

The biometrician plays an essential role in working out compromises between scientific goals and project resources. His/her major contribution consists in quantitative arguments concerning the

feasibility of a project. The biometrician is also crucial in selecting the most appropriate study design and offering effective statistical methodologies to meet the project's objectives (e.g. observational versus experimental, superiority versus non-inferiority or equivalence, parallel groups versus within patient controls, mono-centric versus multi-centric, multivariate versus univariate).

It is important, that in this phase of the project, relevant guidelines are identified and brought to the attention of all participating researchers.

The biometrician is responsible for establishing measures which can achieve maximum objectivity in the planned projects (selection procedures, randomisation, blinding,...).

It is also important that, during this project phase, the biometrician defines his/her role in the project management, i.e. his/her responsibilities during planning, data collection, analysis, and writing study reports. In order to ensure smooth co-operation with the other project partners his/her responsibilities should be well recognised and fully documented.

The manufacturing industry has come to recognise, albeit gradually, that quality control needs to be built in from the start rather than the failures being discarded [4]. It is one intention of this paper to support the progress of a similar process in academically managed medical research projects.

4 Study Design, Writing a Project Protocol

Having screened the relevant information to shape the project ideas, it is important to make them clear and unambiguous. A project protocol has to be written with a detailed description of the study design and all processes (measurements and logistics) related to the project, with clearly defined and accepted endpoints, inclusion and exclusion criteria, plans for interim analyses, appropriate and effective statistical analysis strategies, handling of drop-outs, etc. Furthermore, possible outcomes of the research project should be discussed and steps taken concerning to the different outcomes defined in the protocol.

The biometrician has to ensure that the protocol gives a clear, realistic and objective description of the procedures of the planned medical research process, which means that he/she should be involved in the design of the project protocol as well as in the review and approval of the entire project protocol. Obviously, the main task of the biometrician is to ensure a sound methodological basis for the project.

The protocol should contain the principal concepts of the planned statistical analysis. In an additional document, the statistical analysis plan, detailed and comprehensive strategies of analysis should be specified. The statistical analysis plan prevents medical professionals from drowning in technical terms and protects the biometrician from useless data torturing [7]. This may be especially helpful in the case of complex analyses. The statistical analysis plan should employ the latest state of the art methodologies. Each step and procedure proposed should be backed by relevant references from the literature.

Besides the GCP guideline [8] which sets standards for a clinical trial protocol there are few guidelines which help one to follow a clear procedure when addressing the relevant biometrical issues (like ICH E9 [9], PSI section 2 [10], CPMP Points to Consider documents on methodological issues [11, 12, 13, 14, 15]).

It is important to emphasize that, even for small medical research projects, a project protocol is mandatory. *Carrying out a sensible study, even on a small scale, is indeed useful, but carrying out an ill designed study in ignorance of scientific principles* [4] *... may lead to an epidemic of harm from spurious associations, unnecessary fears and unfulfilled promises of benefit* [16].

5 Data Collection and Data Management

The analysis of data from research projects is only valid and reliable if it is based on high quality data. The biometrician, therefore, has to help ensure the adequate quality of the data on which the analysis is later performed. Consequently, it is necessary that the biometrician can rely on adherence to processes which guarantee high quality data or he/she has to be involved in the shaping and controlling of the processes related to data collection, data coding and data storage.

The data collection and data management processes benefit from pre-defined and established standard operating procedures which determine the quality standards applicable to the research project. The biometrician should insist that plans are in place to control the quality of the data such as review of the source data, plausibility checks, queries, outlier detection, etc.

6 Tasks During an Ongoing Project

It is essential that the biometrician have access to and actively participate in key processes of an ongoing medical research project (meetings of researchers, reports of steering committees, reports of advisory boards). If applicable, the biometrician should prepare relevant reports on the progress of the project. His/her responsibilities and duties should have been well described in the project development plan.

Co-workers should be reminded to inform him/her about emerging and unforeseen problems related to the data acquisition, the measurement process, etc. If interim analyses are planned - a very confidential process with the potential to stop a project prematurely - it will be necessary for the biometrician (as the person that has access to information on the subjects' treatment allocation or as member of an *Efficacy and Safety Data Monitoring Board* [17]) to receive the required information in time and of sufficient quality.

The biometrician can not simply hope to be well informed, but will have to actively establish the necessary communication networks.

7 Statistical Analysis

Every analysis of research data should be considered to be published. The biometrician has to help to ensure that the intention to publish does not introduce bias in his/her analysis.

The statistical analysis has to follow the study protocol and the statistical analysis plan. The statistical analysis plan is intended to give a comprehensive and detailed description of the methods and presentation of data analyses proposed for a project, in order to avoid post hoc decisions that may affect the interpretation of the data collected. A sketch of the statistical analysis plan should already be specified in the project protocol, a sufficiently detailed version has to be finalised prior to data analysis, or, when appropriate, prior to unblinding (see ICH E9 [9]).

The statistical report is part of the research project report. Its form should follow general standards (i.e. ICH E3 [18]) and should clearly describe the design and conduct of the research project as well as results and consequences of all interim analyses and the final analysis. Changes in the statistical analysis plan should be justified and fully documented. Numerical findings should correspond to and be supported by graphical presentations. The analysis should provide evidence that the relevant methodological (formal) requirements were met by applying techniques of model assessment and model diagnosis. Apart from a correct description of the statistical methodology employed in the analysis, the statistical report should present the findings in lay-language.

Concerning quality control, the biometrician should be responsible for ensuring the accuracy and validity of computer programs used in statistical analyses. All procedures employed in statistical analyses should be documented. The documentation should be sufficiently comprehensive to ensure that the analyses can be reproduced.

8 Presentation of Study Results, Interpretation, Publication

Standards for publications have been established, for example, to support the preparation of systematic reviews and meta-analyses which require standardised high quality information sources. Depending on the type of the research project, there are different guidelines on how to present the study results (for example: ICH E3, CONSORT statement [19] for publication of randomised clinical trials, QUOROM statement [20] for publication of meta-analyses).

The biometrician should review all presentations or interpretations of the data analyses (e.g. publications, study reports, integrated summaries, expert reports, promotional material, management meetings and discussions with regulatory authorities, posters, abstracts, oral scientific presentations). He/she should also ensure that data are presented in an unbiased way, that any assumptions in the analyses are clearly stated and that the limitations of the methodology are taken into account. The project development plan should stipulate that no material be published without the biometrician's consent.

When presenting the results, the principle of risk perception has to be taken into consideration. At present, it is not usual for authors to think about how people will react when they are confronted with new findings. It is often not clear, however, how to present data to have an impact on medical practice. This aspect is often neglected by the biometrician who prepares tables and figures, as well as by the medical writer who puts the analysed data into an appropriate medical context [21].

9 Accessibility of Original Data and Analysis Procedures, Fraud

Recent cases of fraud in medical research have attracted considerable media attention, but relatively little reaction from the biostatistical community [22].

In the Internet era, it is surprising that in many medical research projects the data, protocol and routines used for statistical analysis are not made public. As genetic research has gained importance, it has become common practice to offer access to the data studied (for example [23]).

The biometrician should stress the necessity to publish the core data to allow others to critically appraise the results. If possible he/she should prepare a data set suitable for the public. Besides preventing fraud this strategy would be very helpful in supporting activities of groups performing meta-analyses and systematic reviews.

10 Ongoing Education

The complexity of the tasks described in sections 2 to 9 necessitates special qualifications for the biometrician. Persons working as biometricians, therefore, should have an appropriate basic education in biostatistics. It is also necessary to be aware of ongoing developments in methodological research and the need to be properly trained. This results in a duty to engage in *permanent education*. Good biometrical practice demands that the biometrician be willing to be trained according to the latest state of the art. It also implies that the relevant scientific societies should organise and offer high quality continuing education [24]. The *appropriately qualified and experienced statistician* [25] is certainly an ideal to be achieved while a well defined profile of this biometrician is still under development.

11 Checklist

This section proposes a checklist which summarizes important aspects of medical research and may be used to assess the quality of an ongoing or finished research project. The formulations are very general to include as far as possible laboratory, animal and clinical research projects.

Project Planning

- Is there a careful and sufficient review of the literature which shows that the research question is of relevance?
- Is there a thorough discussion of project feasibility?
- Is the research hypothesis clearly formulated?
- Are the responsibilities within the project management clearly defined?

Protocol

- Is the planned study population and the chosen design appropriate?
- Is the study population sufficiently and clearly defined through inclusion and exclusion criteria?
- Are the processes involved in answering the relevant questions sufficiently and clearly described?
- Are the laboratory methods described in an unambiguous way?
- Are blinding procedures necessary and, if needed, well described?
- Does the assignment of *study conditions* follow appropriate rules (i.e randomisation procedure)?
- Is the research hypothesis operationalised? Are the primary and secondary outcome measure(s) and the minimal important difference(s) clearly defined?
- Are the statistical methods appropriate to answer the research question?
- Is there justification for the study size?
- Are prospectively defined stopping rules formulated?
- Is there a thorough risk-benefit discussion?
- Are the different ways of interpreting the results clarified?
- Are all relevant guidelines taken into account and incorporated into the research project?
- Is there an agreement and/or a strategy of how to publish the data?

Ethical concerns

- Is the research submitted to an appropriate ethical review?
- Is the study approved by the responsible ethical committee?

Data Collection and Data Management

- Are relevant SOPs available?
- Are there well established quality control procedures?

Tasks during an ongoing project

- Is the communication between relevant project partners institutionalised (steering committee, data monitoring and safety board - DMSB)?

- Is the biometrician sufficiently integrated into this communication structure?
- Has the biometrician fast access to ongoing processes? Is the information available in time and with sufficient quality?
- Is the ongoing project reported to relevant registries?

Statistical analysis

- Does the analysis follow the protocol and the statistical analysis plan?
- Are the inferential statistics appropriately performed?
- Are the tools used of high quality and according to the state of the art?
- Are relevant summaries given?
- Does the statistical report follow current standards of presentation?

Presentation of Study Results, Interpretation, Publication

- Does the interpretation of results follow the rules determined in the protocol?
- Does the presentation follow international guidelines?
- Are protocol deviations from the planned project well described, together with the reasons?
- Are the results presented in an unambiguous and understandable way?
- Is there a clear separation between the analysis as planned and the analysis as executed during the study?
- Does the biological or medical interpretation of the results correspond to the figures given in the statistical report?
- Are specific interpretations of study findings stated, including sources of bias and imprecision (internal validity)?
- Is external validity discussed?
- Is a general interpretation of the data in light of the totality of the available evidence given?
- Are the data and applied analysis procedures available?
- Is there compliance with the publication strategies announced in the protocol?

12 References

1. Alberts B, Shine K (1994) *Scientists and the integrity of research*, Science, 266, 1660-1661.
2. Foster C. (1995) *Why do research ethics committees disagree with each other?* J R Coll Physicians Lond 1995;29:315-8.
3. Victor N (1999) *Prüfung der wissenschaftlichen Qualität und biometriespezifischer Anforderungen durch die Ethikkommission*, MedR, 1999, 408-412.
4. Altman DG (1994), *The scandal of poor medical research*, BMJ, 308, 283-284.
5. Grimes DA, Schulz KF (2002) *An overview of clinical research: the lay of the land,* The Lancet, 359, 57-61.
6. Chalmers I (2001) *Using systematic reviews and registers of ongoing trials for scientific and ethical trial design, monitoring, and reporting*, In: Egger M, Smith GD, Altman DG (2001) *Systematic reviews in health care*, BMJ Books, London, 429-443.
7. Mills JL (1993) *Data torturing*, N Engl. J. Med, 329, 1196-9.
8. Commission of the European Communities: CPMP Working Party on Efficacy of Medicinal Products. Notes for guidance on good clinical practice for trials on medicinal products in the European Community. Brussels: CEC, 1990.
9. No authors listed (1999) *ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group*. Stat Med, 18(15):1905-42.
10. PSI Statisticians in the Pharmaceutical Industry (1998) *Guidelines for Standard Operating Procedures for Good Statistical Practice in Clinical Research*. Drug Information Journal 32, 665-682.

11. CPMP/EWP/2863/99 Points to Consider on Adjustment for Baseline Covariates (Released for Consultation December 2001)
12. CPMP/EWP/1776/99 Points to Consider on Missing Data (Adopted November 2001)
13. CPMP/EWP/908/99 CPMP Points to Consider on Biostatistical/Methodological issues arising from recent CPMP discussions on Licensing Applications: Adjustment for Multiplicity and Related Topics (Released for Consultation July 01)
14. CPMP/2330/99 Points to Consider on Application with 1.) Meta-analyses and 2.) OnePivotal study (Adopted by CPMP May 2001)
15. CPMP/EWP/482/99 Points to Consider on Switching between Superiority and Non-inferiority (Adopted July 2000)
16. Bogardus ST Jr, Concato J, Feinstein AR (1999) *Clinical epidemiological quality in molecular genetic research: the need for methodological standards*, JAMA, 281 (20):1919-26.
17. Withehead J (1999) *On being the statistician on a Data and Safety Monitoring Board*, Stat Med, 18 (24), 3425-34.
18. No authors listed (1993) ICH Topic E3: Structure and content of clinical study reports, MCA EuroDirect Publication N0. 137/95, EuroDirect Publication Office, London.
19. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, Pitkin R, Rennie D, Schulz KF, Simel D, Stroup DF (1996) *Improving the quality of reporting of randomized controlled trials. The CONSORT statement*. JAMA, 276 (8):637-9.
20. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF (1999) *Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses.* Lancet, 354 (9193):1896-900.
21. Shannon HS, JADA A (1998) *Risk assessment and clinical decision making,* 3852-3857, In: Armitage P, Colton Th, *Encyclopedia of biostatistics*, Wiley, New York.
22. Buyse M et al (1999) *The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials*, SIM, 18, 3435-3451.
23. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, Boldrick JC, Sabet H, Tran T, Yu X, Powell JI, Yang L, Marti GE, Moore T, Hudson J Jr, Lu L, Lewis DB, Tibshirani R, Sherlock G, Chan WC, Greiner TC, Weisenburger DD, Armitage JO, Warnke R, Staudt LM, et al. (2000) *Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling.* Nature, 403 (6769):503-11.
24. Victor N, Holle R et al. (1996). *Empfehlungen der GMDS zur Bildung und Ausbildung in Medizinischer Biometrie.* Inf. Biom. Epidem. Med. Biol. 27, 1-23.
25. Morgan D, Bacchieri A, Bay C, Cobo E, van Ewijk P, Huitfeldt B, Lemarié J-Ch, Malbecq W, Maurer W, Morse P, Nowak H, Trampisch H-J (1999) *Qualified statisticians in the European pharmaceutical industry: report of an EFSPI working group*, DIA Journal, vol 33, pp 407-415.

13 National and international laws and guidelines

http://www.pharmig.or.at/pharmig/amg/amg-inhalt-njs.htm (Arzneimittelgesetz (AMG))
http://www.dimdi.de/germ/mpg/mpg.htm (Medizinproduktegesetz (MPG))
http://www.cirp.org/library/ethics/helsinki/ (Declaration of Helsinki)
http://www.ich.org/pdfICH/e3.pdf (ICH E3, Structure and Content of Clinical Study Reports)
http://www.ich.org/pdfICH/e6.pdf (ICH E6, Guideline for Good Clinical Practice (GCP))
http://www.ich.org/pdfICH/e9.pdf (ICH E9, Statistical Principles for Clinical Trials
http://www.emea.eu.int/index/indexh1.htm (Evaluation of Medicinal Products)
http://www.consort-statement.org/ (CONSORT statement)
http://image.thelancet.com/lancet/extra/QUORUMpdf.pdf (QUOROM statement)
http://www.gmds.de/texte/publikationen/publikationen.html (Memorandi der GMDS e.V.)