**Proposal
Statistics Seminar**

**Statistical Design and Analysis of Analytical Performance Evaluation
Experiments according CLSI**

Contents

1 Introduction

1.1 Presentation of ACOMED statistik

ACOMED statistik, Leipzig, is a company founded by Dr. Thomas Keller in 2003. It offers services in statistical design and evaluation of experiments in life sciences and clinical studies. Customers include companies in the pharmaceutical and diagnostics industry as well as research groups from universities and other public research institutes throughout Europe (focus on Germany and Switzerland) and US.

Statistical services within the design and evaluation of method validations (analytical performance evaluation) as well as diagnostic clinical studies (clinical performance evaluation) are a focus of our work, especially in view of the EU regulation 2017/746.

Dr. Thomas Keller (ACOMED statistik, Leipzig) can refer to excellent references. Please refer to the list of references and publications.

Dr. Keller is a physicist by profession (focus on biophysics) and before founding ACOMED statistik he worked as scientific assistant at Leipzig University and as the head of research and development in a biotech company, where he was significantly involved in the development of a point-of-care device. Therefore, Dr. Keller can refer to practical experience in laboratory work such as measuring, pipetting etc. and the corresponding quality assurance.

The comprehensive experience gained in interdisciplinary cooperation with physicians and scientists from the life sciences is incorporated into the statistics seminars offered by Dr. Keller.

Dr. Thomas Keller has been a member of several CLSI subcommittees (EP09, EP25, EP40) and is a member of the IFCC working group "Commutability".

1.2 Statistics Seminars

The statistics seminars are aimed at physicians and scientists in the field of life sciences. As a rule, the seminars are offered as in-house seminars for companies and laboratories. Since 2019 the seminars provided mainly as webinars, so labs and IvD companies from all over the world (e. g. New Zealand, South Africa) belong to the customers.

Dr. Keller also participates in seminar series (BB-Life Berlin-Brandenburg, FORUM-Institut Heidelberg, ProCell-Academy Heidelberg, Biosaxony).

2 What you can expect from the seminar

2.1 Specific characteristics

The following characteristics distinguish the seminars:

- "Statistics without formulas." Of course, formulas are also presented, but the seminars are designed in such a way that the basic understanding of statistical facts should be awakened.
- "Statistics - no foreign language". The experience of multi-professional teams from laboratories and clinics means that statistical data is communicated in the language of the user. Statistical terms are of course presented, but only used to the extent necessary.
- "Data of the audience as examples". It has proven itself to ask questions, application examples and data sets of customers and listeners in advance and to use them as examples in the seminars. This increases the target-orientation of the seminar contents, the motivation of the listeners and the learning effect.
- Small MS-Excel^{TM}-tools developed by ACOMED statistik are used within the seminar by the participants to perform simple calculations.

2.2 Participants

The seminars are aimed at scientists and laboratory staff from IVD companies and clinical laboratories. The audience includes those responsible for quality assurance and regulatory affairs, too. The seminar is also suitable for statisticians who want to familiarize themselves with the specifics of statistical analyses of method validation experiments.

2.3   Aim of the seminar

The aim of the seminar is to enable the participants to evaluate and classify the results of method validation experiments from a statistical point of view. They know the necessary statistical concepts and methods which are necessary for the design and analysis of method validation experiments. After the seminar, they will be able to set up corresponding experimental protocols.

With regard to analyses, the participants have the basis to familiarise themselves with the practical aspects, but additional effort, daily practice etc. are required for this.

2.4   Example data

A broad spectrum of data from method validation experiments is available.

However, we prefer to use sample data sets provided by the customer in advance during the seminar.

2.5   Practical aspects

It has proven itself to split full-day seminars over two half days (afternoon + following morning). As a rule, there are no additional costs.

Typically 3 – 16 participants are expected.

It is preferred if the scripts are printed by the customer.

Certificates are issued.

The seminars can be presented in German (preferred) or in English[1].

2.6   Software

The seminars can be combined with software training courses (Excel, Analyse-It, R etc.). As a rule, the customer is responsible for providing the hardware and software.

2.7   Software training (Analyse-It™)

In terms of analysis of analytical performance studies and method validation experiments, Dr. Keller provides software trainings for software Analyse-It™.

These software trainings contain statistical and methodological background as listed in chapter 3.3 as well.

Dr. Keller is mentioned as an official partner of the website of Analyse-It™. It would be possible to use temporary licenses within the seminar.

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[1] (please note somewhat limited skills in English language)

3   Contents of the seminar

3.1   Basic statistics

Statistical description of data (mean, median, standard deviation, graphical representation) parametric vs non-parametric approaches

Statistical estimation, standard error, confidence interval

Statistical proof (testing) by confidence intervals (test of a difference vs. test of equivalence or non-inferiority

3.2   Advanced statistics

Regression methods (for method comparison, linearity, stability)

ANOVA, esecially random effects ANOVA for estimation of variance components (for evaluation of precision and specific compounds (intra- and inter-factor precision)

3.3   Statistics of method validation experiments

Typically, 3 of the following method validation experiments can be presented at 1 day.

Please chose according your interests.

3.3.1   Method comparison acc. CLSI EP09

Introduction in bias, trueness and other terms

Method comparison – application of difference plots

Method comparison – application of regression methods

Proof of equivalence as a typical aim of method comparison experiments and its statistical implementation (equivalence testing).

Setup of experiments, sample size

Analysis of data, examples

Software solution (Analyse-It™, Medcalc™, MS Excel™-tools)

Note: Dr. Keller was a member of the CLSI subcommittee for development of version A3 of EP09 guideline.

3.3.2   Analytical performance of qualitative methods (focus method comparison)

Statistics of categorically (binary) scaled data

Method comparison: Agreement, consistency, kappa-statistics, respective confidence intervals

Precision for qualitative measurants

Diagnostic performance measures (sensitivity, specificity, predictive values, diagnostic likelihood ratios)

Software solutions (Analyse-It™, ACOMED statistic tools)

3.3.3   Precision acc. CLSI EP05

Introduction in precision, repeatability, reproducibility

Setup of the multilevel experiment, sample size

Application of random effects ANOVA to estimate variance components ($\rightarrow$ to calculate repeatability, other precision components and reproducibility from 1 experiment)

Analysis of data, examples

Software solution (Analyse-It™, MS Excel™-tools, VFP, R)

3.3.4   Detection Capability acc. CLSI EP17

Introduction into terms (Limit of Blanks, Limit of Detection, Limit of Quantitation)

Statistical background (parametric vs non parametric description of data)

Analysis of data, examples

Software solutions (Analyse-It™)

3.3.5   Reference intervals acc. CLCI EP28

Statistical background (parametric vs non parametric description of data)

Experimental requirements and setup, sample size

Uncertainty of reference limits

Analysis of data, examples

Software solution (Analyse-It™)

3.3.6   Linearity acc. CLSI EP06

Statistical background (linear and polynomial regression)

Analysis of data, examples

Software solution (Analyse-It™, MS Excel™)

3.3.7   Carry over

Carry over as a non inferiority problem

Analysis of data

Software solution

3.3.8   Stability acc. EP25

Evaluation of stability as a statistical equivalence problem

Application of a regression approach

Software solution

Note: Dr. Keller was a member of the CLSI subcommittee for development of version A3 of EP25 guideline.

3.3.9   Commutability acc. EP14 and EP30

Evaluation of commutability as a statistical equivalence problem

Statistical approaches

Note: Dr. Keller is a member of the IFCC working groups for development of respective recommendations

3.3.10   Other topics

If you would like training on other topics, we would be happy to check whether we can also offer seminars on this subject.

4   Publications related to this topic

Lambert C, Demirel GY, **Keller T**, Preijers F, Psarra K, Schiemann M, Özçürümez M, Sack U (2020). Flow Cytometric Analyses ofLymphocyte Markers in Immune Oncology: A Comprehensive Guidance for Validation Practice According to Laws and Standards. Front. Immunol. 11:2169.

Macagno A, 1, Athanasiou A, Wittig A, Huber R, Weber S, **Keller, T**, Rhiel M, Golding B, Schiess R (2020). Analytical performance of thrombospondin-1 and cathepsin 1 D immunoassays part of a novel CE-IVD marked test as an aid in the diagnosis of prostate cancer. PLOS One, 15:e0233442. Link

Klocker H, Golding B, Weber S, Steiner E, Tennstedt P, **Keller T**, Schiess R, Gillessen S, Horninger W, Steuer T (2020): Development and validation of a novel multivariate risk score to guide biopsy decision for the diagnosis of clinically significant prostate cancer. BJUI Compass. 2020;00:1–6. https://doi.org/10.1002/bco2.8. Link

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Korn S, Wilk M, Voigt S, Weber S, **Keller T**, Buhl R (2020): Measurement of Fractional Exhaled Nitric Oxide: Comparison of Three Different Analysers. Respiration. 99,1-8. doi: 10.1159/000500727.

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Budd JR, Weykamp C, Rej R, MacKenzie F, Ceriotti F, Greenberg N, Camara JE, Schimmel H, Vesper HW, **Keller T**, Delatour V, Panteghini M, Burns C, Miller WG (2018). IFCC Working Group Recommendations for Assessing Commutability Part 3: Using the Calibration Effectiveness of a Reference Material. Clin Chem 64: 465-74

Varga Z, Lebeau A, Bu H, Hartmann A, Penault-Llorca F, Guerini-Rocco E, Schraml P, Symmans F, Stoehr R, Teng X, Turzynski A, von Wasielewski R, Gürtler C, Laible M, Schlombs K, Joensuu H, **Keller T**, Sinn P, Sahin U, Bartlett J, Viale G (2017). An international reproducibility study validating quantitative determination of ERBB2, ESR1, PGR, and MKI67 mRNA in breast cancer using MammaTyper®.Breast Cancer Research. Breast Cancer Res. 2017 May 11;19(1):55. doi: 10.1186/s13058-017-0848-z. Download

Lorenz K, **Keller T**, Noack B, Freitag A, Netuschil L, Hoffmann T (2016). Evaluation of a novel point-of-care test for active matrix metalloproteinase-8: agreement between qualitative and quantitative measurements and relation to periodontal inflammation. J Periodontal Res. DOI: 10.1111/jre.1239

Häckel R, Gurr E, **Keller T** (2016): Permissible measurement uncertainty in the lower part of measurement intervals, J Lab Med 40, 271-77

Keller T, Brinkmann T (2014). Proposed Guidance for Carryover Studies, Based on Elementary Equivalence Testing. Clin. Lab 7,1153-61

Goossens K, De Grande LA, **Keller T,** Weber S, Thienpont LM (2014). Verification of reference intervals by the C28 protocol - The alpha error/power trade-off. Clin Chim Acta 436, 18-19

Zegers I, Beetham R, Keller T, Sheldon J, Bullock D, MacKenzie F, Trapmann S, Emons H and Schimmel H (2013). The Importance of Commutability of Reference Materials Used as Calibrators: The Example of Ceruloplasmin. Clin Chem. 59:1322–9

Titiz I, Laubinger M, **Keller T**, Hertrich K and Hirschfelder U (2012): Repeatability and reproducibility of landmarks — a three-dimensional computed tomography study. Eur J Orthod. 34, 276-86

Hoffmann T, Bruhn G, Lorenz K, **Keller T**, Netuschil L (2011). Agreement between qualitative aMMP-8 Chair side and quantitative ELISA Test. J Dent Res 90 (Spec Iss A), Abstr.# 323

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Auclair G, **Keller T**, Sinha P, Sheldon J, Rota F, Schimmel H, Zegers I (2011): Commutability study on ERM-DA472/IFCC, C-reactive protein in human serum. CCLM 49, S804

Fillée1 C, **Keller T**, Ketelslegers JM (2011): Vitamin-D related parathyroid hormone reference ranges and their impact on the diagnosis of mild primary hyperparathyroidism. CCLM 49, S423

Katzorke T, Faye SA, **Keller T** (2011): AMH GEN II: A Comparison of results versus DSL AMH ELISA and reference interval data. CCLM 49, S421

Zegers I, **Keller T**, Schreiber W, Sheldon J, Albertini R, Blirup-Jensen S, Johnson M, Trapmann S, Emons H, Merlini G, Schimmel H (2010): Characterisation of ERM-DA470k/IFCC for 12 serum proteins. Clin Chem, 56:1880-1888

Zemlin AE, Essack Y, Rensburg M, **Keller T**, Brinkmann T (2010): Stability of Red Blood Cell Folate in Whole Blood and Haemolysate. Clin. Lab 56: 391-396

Keller T, Brinkmann T (2010): Statistical Test for Equivalence and Non-Inferiority in Analysis of Method Validation and Comparison Experiments: Application in Assessment of Carry-over. Clin Chem; 56 Suppl.: A222

Weber S, **Keller T** (2009): Statistical Analysis of Commutability Experiments: Application of equivalence test as an advantageous approach. CCLM 47, A22.

Keller T, Weber S (2009): Statistical Test for Equivalence in Analysis of Commutability Experiments. CCLM 47, 376-377.

Keller T, Brinkmann T (2009): Statistical Test for Equivalence and Noninferiority in Analysis of Method Validation and Comparison Experiments. Application in Assessment of Carry-Over. CCLM 47, 356-357.

5 References (statistical design and analysis)

If not other stated, Germany is the location.

5.1 Universities and public research organizations

Charité Berlin, Pediatric Oncology, Urologa

CLSI Subcommittees EP9 and EP25, Utah, USA

Fraunhofer Institute for Celltherapy and Immunology, Leipzig

IRMM (Institute for reference materials, Gent, Belgien)

University of Leipzig, Immunology

University of Düsseldorf, Pediatric Oncology

University of Dresden, Clinical lab (gynaecology)

University of Erlangen, Clinical lab (pediatrics),

University of Essen, Clinical Lab (gynaecology)

University of Gent (Belgium), Clinical lab

5.2 IVD-companies

AdnaGen AG, Hannover

Bayer Diagnostics GmbH, Fernwald (now Siemens AG)

Beckmann Coulter GmbH (Krefeld, and Nyon/Schweiz)

Brahms GmbH, Berlin-Henningsdorf

Dentognostics GmbH

GILUPI GmbH, Potsdam

Greiner Bio-One GmbH (Frickenhausen, sowie Rainbach/Österreich)

Lophius Biosciences GmbH, Regensburg

LifeCodexx AG, Konstanz

LS Labor AG, Bad Bocklet (Laboratory for pharmaceutical industry)

MTM laboratories AG (now Roche Diagnostics)

R-Biopharm AG, Darmstadt

Sysmex Europe GmbH, Norderstedt

And others

6   References (statistical training)

Antrum Biotech (Ply) Ltd., Capetown, South Africa

Beckmann Coulter GmbH, Krefeld and Nyon/Schweiz

BB Life, Berlin

Biostats LLC, Las Vegas, USA

Biosaxony academy, Dresden/Leipzig

Boehringer Ingelheim Pharma Gmbh & Co. KG (Biomarker-Unit), Ingelheim

Charles River, Freiburg

FORUM-Institut, Heidelberg

Fachhochschule Kärnten, Klagenfurt, Austria

Fraunhofer Institute for Celltherapy and Immunology, Leipzig

Lonza Cologne GmbH, Cologne

IBBL (Integrated BioBank of Luxembourg)

INSTAND e.V., Düsseldorf

mibe Arzneimittel GmbH, Brehna

Pictor, Auckland, New Zealand

ProGen Biotechnik GmbH, Heidelberg

R-Biopharm AG, Darmstadt

Sysmex Europe GmbH, Norderstedt

TRM Leipzig

TU München

Vet Med Labor GmbH, Ludwigsburg

and others