

### PERSONAL INFORMATION **Norbert Benda**

#### WORK EXPERIENCE

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- February 2010- Present **Head of Biostatistics and Special Pharmacokinetics Unit**  
BfArM (Federal Institute for Drugs and Medical Devices) (Germany)  
Managing Biostatistics and Special Pharmacokinetics Unit, biostatistical assessment of European and national German drug applications, biostatistical support in scientific advices, biostatistical input to guidelines, biostatistical input to clinical and methodological research projects
- November 2006-January 2010 **(Senior) Expert Statistical Methodologist**  
Novartis Pharma AG (Switzerland)  
Development and application of novel statistical methodologies (dose-finding, adaptive designs, longitudinal data analysis, missing data, optimal design), methodological support for Trial and Program Statisticians, clinical scenario evaluations (simulations) for clinical trial planning, internal training courses in statistics
- July 1997-October 2006 **Statistician**  
Schering AG (Germany)  
Statistical design and analysis of clinical studies (phase I - IV), statistical consultant for preclinical and clinical development, project statistician for international drug development projects, member of the Global Pharmacometrics Team
- October 1993-July 1997 **Research Assistant**  
University of Tübingen, Department of Medical Biometry (Germany)  
Statistical consultant in statistics for medical PhD students and researchers, lectures in medical statistics, design and evaluation of medical studies, research projects in ophthalmology
- April 1989-September 1993 **Research Assistant**  
Free University of Berlin, Institute of Mathematics (Germany)  
Research in mathematical statistics (experimental design), lectures in statistics for students of mathematics and biology

#### EDUCATION AND TRAINING

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- April 1989-December 1992 **Doctorate in Mathematics (Dr. rer. nat.)**  
Institute of Mathematics, Free University of Berlin (Germany)
- October 1982-October 1988 **Diploma in Mathematics**  
Technical University Aachen (RWTH Aachen) (Germany)

#### ADDITIONAL INFORMATION

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**Expertise** Biostatistics  
Clinical Trials  
Epidemiology

- Publications**
1. Huber C, Friede T, Stingl JC, Benda, N (2021). Classification of companion diagnostics: A new framework for biomarker driven patient selection. Therapeutic Innovation & Regulatory Science. Published online 28 Nov 2021, <https://link.springer.com/article/10.1007%2Fs43441-021-00352-2>.
  2. Huber C, Benda N, Friede T (2021). Subgroup identification in individual participant data meta-analysis using model-based recursive partitioning. Adv Data Anal Classif (2021). Published online 14 Aug 2021. <https://doi.org/10.1007/s11634-021-00458-3>

3. Mutze T, Salem S, Benda N, Schmidli H, Friede T (2020). Blinded continuous information monitoring of recurrent event endpoints with time trends in clinical trials. *Statistics in Medicine* 39(27): 3968-3985.
4. Kesselmeier M, Benda N, Scherag A (equal contributions of all authors) (2020). Effect size estimates from umbrella designs: handling patients with a positive test result for multiple biomarkers using random or pragmatic subtrial allocation. *PLOS One*. Published online: 14 Aug 2020.
5. Stallard N, Hampson L, Benda N, Brannath W, Burnett T, Friede T, Kimani PK, Koenig F, Krisam J, Mozgunov P, Posch M, Wason J, Wassmer G, Whitehead J, Williamson SF, Zohar S, Jaki T (2020). Efficient Adaptive Designs for Clinical Trials of Interventions for COVID-19. *Statistics in Biopharmaceutical Research*. Published online (early view): 29 Jul 2020.
6. Benda N, Haenisch B (2020). Enrichment designs using placebo nonresponders. *Pharm Stat*. 19(3):303-314.
7. Prus M, Benda N, Schwabe R (2020). Optimal Design in Hierarchical Random Effect Models for Individual Prediction with Application in Precision Medicine. *Journal of Statistical Theory and Practice* 14(2).
8. Holtkamp F, Gudmundsdottir H, Maciulaitis R, Benda N, Thomson A, Vetter T (2020). Change in Albuminuria and Estimated GFR as End Points for Clinical Trials in Early Stages of CKD: A Perspective From European Regulators. *Am J Kidney Dis*. 75(1):6-8.
9. Zapf A, Stark M, Gerke O, Ehret C, Benda N, Bossuyt P, Deeks J, Reitsma J, Alonzo T, Friede T (2020). Adaptive trial designs in diagnostic accuracy research. *Stat Med*. 39(5):591-601.
10. Hampel H, Vergallo A, Afshar M, Akman-Anderson L, Arenas J, Benda N, Batrla R, Broich K, Caraci F, Cuello AC, Emanuele E, Haberkamp M, Kiddle SJ, Lucia A, Mapstone M, Verdooner SR, Woodcock J, Lista S (2019). Blood-based systems biology biomarkers for next-generation clinical trials in Alzheimer's disease. *Dialogues Clin Neurosci*. 21(2):177-191.
11. Huber C, Benda N, Friede T (2019). A comparison of subgroup identification methods in clinical drug development: Simulation study and regulatory considerations. *Pharm Stat*. 18(5):600-626.
12. Graf von Kielmansegg S, Benda N, Grass G, Sudhop T (2019). Die Rolle von Ethikkommissionen bei der Bewertung klinischer Arzneimittelprüfungen [Ethics committees in clinical trials involving medicinal products]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 62(6):706-712. German.
13. Unkel S, Amiri M, Benda N, Beyersmann J, Knoerzer D, Kupas K, Langer F, Leverkus F, Loos A, Ose C, Proctor T, Schmoor C, Schwenke C, Skipka G, Unnebrink K, Voss F, Friede T (2019). On estimands and the analysis of adverse events in the presence of varying follow-up times within the benefit assessment of therapies. *Pharm Stat*. 18(2):166-183.
14. Friede T, Posch M, Zohar S, Alberti C, Benda N, Comets E, Day S, Dmitrienko A, Graf A, Gunhan BK, Hee SW, Lentz F, Madan J, Miller F, Ondra T, Pearce M, Rover C, Toumazi A, Unkel S, Ursino M, Wassmer G, Stallard N (2018). Recent advances in methodology for clinical trials in small populations: the InSPiRe project. *Orphanet J Rare Dis*. 25:13(1):186. Review.
15. Benda N (2018). Book review: Quantitative decisions in drug development. Chuang-Stein, Christy and Kirby, Simon (2017). *Biometrical Journal* 61, 1090-1091.
16. Hampel H, Vergallo A, Aguilar LF, Benda N, Broich K, Cuello AC, Cummings J, Dubois B, Federoff HJ, Fiandaca M, Genthon R, Haberkamp M, Karran E, Mapstone M, Perry G, Schneider LS, Welikovitsh LA, Woodcock J, Baldacci F, Lista S (2018). Alzheimer Precision Medicine Initiative (APMI). Precision pharmacology for Alzheimer's disease. *Pharmacol Res*. 130:331-365.
17. Benda N, Brandt A (2018). Regulatory issues with multiplicity in drug approval: Principles and controversies in a changing landscape. *J Biopharm Stat*. 28(1):3-9.
18. Benda N, Burkner PC, Freise F, Holling H, Schwabe R (2017). Adaptive designs for quantal dose-response experiments with false answers. *Journal of statistical theory and practice* 11, 361-374.
19. Benda N (2017). Book review: Modern Adaptive Randomized Clinical Trials. O. Sverdlov (ed.) (2016). *Biometrical Journal* 59, 1402-1403.
20. Leuchs AK, Brandt A, Zinserling J, Benda N (2017). Disentangling estimands and the intention-to-treat principle. *Pharm Stat* 16, 12-19.
21. Klaus V, Bastek H, Damme K, Collins LB, Frotschl R, Benda N, Lutter D, Ellinger-Ziegelbauer H, Swenberg JA, Dietrich DR, Stemmer K (2017). Time-matched analysis of DNA adduct formation and early gene expression as predictive tool for renal carcinogenesis in methylazoxymethanol acetate treated Eker rats. *Arch Toxicol* 91, 3427-3438.

22. Musuamba FT, Manolis E, Holford N, Cheung S, Friberg LE, Ogungbenro K, Posch M, Yates J, Berry S, Thomas N, Corriol-Rohou S, Bornkamp B, Bretz F, Hooker AC, Van der Graaf PH, Standing JF, Hay J, Cole S, Gigante V, Karlsson K, Dumortier T, Benda N, Serone F, Das S, Brochot A, Ehmann F, Hemmings R, Rusten IS (2017). Advanced Methods for Dose and Regimen Finding During Drug Development: Summary of the EMA/EFPIA Workshop on Dose Finding (London 4-5 December 2014). *CPT Pharmacometrics Syst Pharmacol* 6, 418-429.
23. Manolis E, Brogren J, Cole S, Hay JL, Nordmark A, Karlsson KE, Lentz F, Benda N, Wangorsch G, Pons G, Zhao W, Gigante V, Serone F, Standing JF, Dokoumetzidis A, Vakkilainen J, van den Heuvel M, Mangas Sanjuan V, Taminiou J, Kerwash E, Khan D, Musuamba FT, Skottheim Rusten I; EMA Modelling and Simulation Working Group (2017). Commentary on the MID3 Good Practices Paper. *CPT Pharmacometrics Syst Pharmacol* 6, 416-417.
24. Hampel H, O'Bryant SE, Castrillo JI, Ritchie C, Rojkova K, Broich K, Benda N, Nistico R, Frank RA, Dubois B, Escott-Price V, Lista S (2016). Precision Medicine - The Golden Gate for Detection, Treatment and Prevention of Alzheimer's Disease. *J Prev Alzheimers Dis* 3, 243-259.
25. Stingl JC, Kaumanns KL, Claus K, Lehmann ML, Kastenmuller K, Bleckwenn M, Hartmann G, Steffens M, Wirtz D, Leuchs AK, Benda N, Meier F, Schoffski O, Holdenrieder S, Coch C, Weckbecker K (2016). Individualized versus standardized risk assessment in patients at high risk for adverse drug reactions (IDrug) - study protocol for a pragmatic randomized controlled trial. *BMC Fam Pract* 26, 17-49.
26. Unkel S, Rover C, Stallard N, Benda N, Posch M, Zohar S, Friede T (2016). Systematic reviews in paediatric multiple sclerosis and Creutzfeldt-Jakob disease exemplify shortcomings in methods used to evaluate therapies in rare conditions. *Orphanet J Rare Dis* 20, 11-16.
27. Leuchs AK, Zinserling J, Brandt A, Wirtz D, Benda N (2015). Choosing appropriate estimands in clinical trials. *Therapeutic Innovation & Regulatory Science* 49, 584-592.
28. Helms HJ, Benda N, Zinserling J, Kneib T, Friede T (2015). Spline-based procedures for dose-finding studies with active control. *Statistics in Medicine* 34, 232-248.
29. Helms HJ, Benda N, Friede T (2015). Point and interval estimators of the target dose in clinical dose-finding studies with active control. *Journal of Biopharmaceutical Statistics* 25, 939-957.
30. Dette H, Kiss C, Benda N, Bretz F (2014). Optimal designs for dose finding studies with an active control. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 76, 265-295.
31. Leuchs AK, Zinserling J, Schlosser-Weber G, Berres M, Neuhauser M, Benda N (2014). Estimation of the treatment effect in the presence of noncompliance and missing data. *Statistics in Medicine* 33, 193-208.
32. Grosshennig A, Benda N, Koch, A (2013). Die Bedeutung von Biomarkern für eine personalisierte Medizin. *Bundesgesundheitsblatt* 56, 1480-1488.
33. Benda N, Bender R (2011). Multiplicity Issues in Clinical Trials. *Biometrical Journal* 53, 873-874. Editorial.
34. Benda N (2010). Model-based approaches for time dependent dose finding with repeated binary data. *Statistics in Medicine* 29, 1096-1106.
35. Benda N, Branson M, Maurer W, Friede T (2010). Modernizing drug development using clinical scenario planning and evaluation. *Drug Information Journal* 44, 299-315.
36. Akacha M, Benda N (2010). The impact of dropouts on the analysis of dose-finding studies with recurrent event data. *Statistics in Medicine* 29, 1635-1646.
37. Benda N, Branson M, Maurer W, Friede T (2009). Clinical Scenario Evaluation - A framework for evaluating competing development strategies. *Drug: Development* 4, 84-88.
38. Benda N, Brannath W, Bretz F, Burger HU, Friede T, Maurer W, Wang SJ (2010). Perspectives on the use of adaptive designs in clinical trials: Part II. Panel Discussion. *Journal of Biopharmaceutical Statistics* 20, 1098-1112.
39. Blode H, Schurmann R, Benda N (2008). Novel ethinyl estradiol-beta-cyclodextrin clathrate formulation does not influence the relative bioavailability of ethinyl estradiol or coadministered drospirenone. *Contraception* 77, 171-176.
40. Benda N, Gerlinger C (2007). Sperm count as a surrogate endpoint for male fertility control. *Statistics in Medicine* 26, 4905-4913.
41. Schmelter T, Benda N, Schwabe R (2007). Some curiosities in optimal designs for random slopes. In: J. Lopez-Fidalgo, J. M. Rodriguez-Diaz and B. Torsney (Hrsg.): *MODA 8 - Advances in Model-Oriented Design and Analysis*. Physica: Heidelberg. 189-195.

42. Rohmel J, Gerlinger C, Benda N, Lauter J (2006). On testing simultaneously non-inferiority in two multiple primary endpoints and superiority in at least one of them. *Biometrical Journal* 48, 916-933.
43. Schurmann R, Blode H, Benda N, Cronin M, Kufner A (2006). Effect of drospirenone on serum potassium and drospirenone pharmacokinetics in women with normal or impaired renal function. *Journal of Clinical Pharmacology* 8,867-875.
44. Entholzner M, Schmelter T, Benda N, Schwabe R (2005). A note on designs for estimating population parameters. *Biometrical Letters* 41, 25-41.
45. Benda N, Gerlinger C, van der Meulen E, and Endrikat J (2004). Sample size calculation for clinical studies on the efficacy of a new contraceptive method. *Biometrical Journal* 46, 141-150.
46. Schurmann R, Holler T, Benda N (2004). Estradiol and drospirenone for climacteric symptoms in postmenopausal women: a double-blind, randomized, placebo-controlled study of the safety and efficacy of three dose regimens. *Climacteric* 7, 189-196.
47. Huppert PE, Lauchart W, Duda SH, Torkler C, Kloska SP, Weinlich M, Benda N, Pereira P, Claussen CD (2004). Chemoembolisation des hepatozellularen Karcinoms: Welche Faktoren bestimmen Therapieansprechen und Überleben? *Fortschritte auf dem Gebiet der Röntgenstrahlen und bildgebenden Verfahren (Rofo)* 176, 375-385.
48. Bachmann G, Sulak PJ, Sampson-Landers C, Benda N, Marr J (2004). Efficacy and safety of a low-dose 24-day combined oral contraceptive containing 20 micrograms ethinylestradiol and 3 mg drospirenone. *Contraception* 70, 191-198.
49. Mielke G, Benda N (2001). Cardiac output and central distribution of blood flow in human fetus. *Circulation* 103, 1662-1668.
50. Lutz S, Dietrich TJ, Benda N, Selig B, Strasburger H, Schiefer U (2001). An explicit no response instead of time-out in automated visual-field testing. *Graefes Archive of Clinical and Experimental Ophthalmology* 239, 173-181.
51. Mielke G, Benda N (2000). Blood flow velocity waveforms of the fetal pulmonary artery and the ductus arteriosus: Reference ranges from 13 weeks to term. *Ultrasound in Obstetrics and Gynecology* 15, 213-218.
52. Mielke G, Benda N (2000). Reference ranges for two-dimensional echocardiographic examination of the fetal ductus arteriosus. *Ultrasound in Obstetrics and Gynecology* 15, 219-225.
53. Benda N, Schiefer U, Dietrich TJ (1999). Models for the description of angioscotomas. *Vision Research* 39, 1889-1896.
54. Franz HBG, Schneider D, Benda N, Erz W, Neuer A, Gonser M (1999). Die unkomplizierte Geburtsverletzung als Risikofaktor analer Inkontinenz? *Zeitschrift für Geburtshilfe und Neonatologie* 203, 24-28.
55. Schiefer U, Benda N, Dietrich TJ, Selig B, Hofmann C, Schiller J (1999). Angioscotoma detection with fundus-oriented perimetry - A study with dark and bright stimuli of different sizes. *Vision Research* 39, 1897-1909.
56. Dietrich TJ, Ata N, Sanger A, Selig B, Schiefer U, Benda N (1999). Age influences asymmetry in differential luminance sensitivity. In: Wall M and Heijl A (Hrsg.): *Perimetry Update 1998/1999*. Kugler Publications: Amsterdam/New York, 223-227.
57. Topka H, Massaquoi SG, Benda N, Hallett M (1998). Motor Skill Learning in Patients with Cerebellar Degeneration. *Journal of the Neurological Sciences* 158, 164-172.
58. Franz HBG, Benda N, Gonser M, Backert IT, Jehle EC (1998). Klinische Auswirkungen der Geburt mit medianer Episiotomie und analer Sphinkterverletzung auf die Stuhlinkontinenz bei Primiparae. *Zentralblatt für Chirurgie* 123, 218-223.
59. Bader P, Beck J, Frey A, Schlegel PG, Hebarth H, Handgretinger R, Einsele H, Niemeyer C, Benda N, Faul C, Kanz L, Niethammer D, Klingebiel T (1998). Serial and quantitative analysis of mixed hematopoietic chimerism by PCR in patients with acute leukemias allows the prediction of relapse after allogeneic BMT. *Bone Marrow Transplantation* 21, 487-95.
60. Enderle MD, Benda N, Schmulling RM, Haering HU, Pfohl M (1998). Preserved endothelial function in IDDM patients, but not in NIDDM patients, compared with healthy subjects. *Diabetes Care* 21, 271-277.
61. Pfohl M, Athanasiadis A, Koch M, Clemens P, Benda N, Haring HU, Karsch KR (1998). Insertion/deletion polymorphism of the angiotensin I-converting enzyme gene is associated with coronary artery plaque calcification as assessed by intravascular ultrasound. *Journal of the American College of Cardiology* 31, 987-91.

62. Maisch C, Hofmann V, Benda N, Luft D (1998). Evaluation of polarographic measurements of basal muscle oxygen tension in type I diabetic patients. *Angiology* 49, 203-210.
63. Benda N, Schwabe R (1998). Designing Experiments for Adaptively Fitted Models. In: Atkinson AC, Pronzato L and Wynn HP (Hrsg.): *MODA 5 - Advances in Model-Oriented Data Analysis*. Physica: Heidelberg, 165-175.
64. Schiefer U, Stercken-Sorrenti G, Dietrich TJ, Benda N (1997). Fundus oriented perimetry (F.O.P.) - A new concept increasing efficiency of visual field examination. In: Wall M and Heijl A (Hrsg.): *Perimetry Update 1996/1997*. Kugler Publications: Amsterdam/New York, 107-109.
65. Benda N, Dietrich TJ, Schiefer U (1997). Fitting Angioscotomas. In: Wall M and Heijl A (Hrsg.): *Perimetry Update 1996/1997*. Kugler Publications: Amsterdam/New York, 207-210.
66. Bruck B, Brehm U, Gugel N, Hanke S, Lutz C, Benda N, Schmahl FW, Haasis R, Hanke H (1997). Gender Specific Differences in the Effect of Testosterone and Estrogen in the Development of Atherosclerosis in Rabbits. *Arteriosclerosis, Thrombosis, and Vascular Biology* 17, 2192-2199.
67. Haber HP, Benda N, Fitzke G, Lang A, Langenberg M, Riethmuller J, Stern M (1997). Colon wall thickness measured by ultrasound: Striking differences in cystic fibrosis patients versus healthy controls. *Gut* 40, 406-411.
68. Bader P, Holle W, Klingebiel T, Handgretinger R, Benda N, Schlegel PG, Niethammer D, Beck J (1997). Mixed hematopoietic chimerism after allogeneic bone marrow transplantation: the impact of quantitative PCR analysis for prediction of relapse and graft rejection in children. *Bone Marrow Transplantation* 19, 697-702.
69. Schiefer U, Benda N, Stercken-Sorrenti G, Dietrich TJ, Friedrich M (1996). Fundus-orientierte Perimetrie. Evaluation eines neuen Gesichtsfeld-Untersuchungsverfahrens bezüglich der Detektion von Angiosknoten. *Klinische Monatsblätter für Augenheilkunde* 208, 62-71.
70. Luft D, Lay A, Benda N, Kort C, Hofmann V, Hardin H, Renn W (1996). Pain Intensity and Blood Pressure Reactions During a Cold Pressor Test in IDDM Patients. *Diabetes Care* 19, 722-725.
71. Benda N (1996). Pre-test Estimation and Design in the Linear Model. *Journal of Statistical Planning and Inference* 52, 225-240.
72. Wabbels B, Schiefer U, Treutwein B, Benda N, Stercken-Sorrenti G (1995). Automated perimetry with bright and dark stimuli, *German Journal of Ophthalmology* 4, 217-221.

**Projects** IMI Projects HARMONY and HARMONY Plus

**Memberships** International Biometric Society  
EMA Biostatistics Working Party

**Other Relevant Information**