Project name:

"In-depth biometric support and analyses of the data from the ABPARO project"

Short title: ABPARO

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Summary

The ABPARO project ("Adjunctive Antimicrobial Therapy of Periodontitis: Long-Term Effects on Disease Progression and Oral Microbiological Colonization (ABPARO)" is a clinical trial about the efficacy of an adjunctive systemic antimicrobial therapy compared to mechanical debridement alone. The trial was designed with regard to the suggestions from current systematic reviews. The simultaneous collection of clinical, microbiological, genetic, psychological and demographic parameters in a population representative sample, made this trial unique. Overall 405 patients finished the trial in December 2011. This is the world largest antibiotic therapy study in periodontology and the first that chose an objective parameter for disease progression ("attachment loss") and true subjective endpoint ("oral health related quality of life"). Initially, the project was funded by the Deutsche Forschungsgemeinschaft (DFG EH 365/1-1), but the funding program ("Sonderprogram Klinische Studien") expires in May 2012. Due to the large amount of various data, we strongly need further the support of a qualified biostatistician, to assure the continuous analyses and publication of this project.

1. Background

Periodontitis is an endemic inflammatory disease caused by a mixed bacterial infection. It is characterized by a severe destruction of tooth-supporting periodontal tissues, i.e., the connective tissue attachment apparatus and alveolar bone ("attachment loss"). Advanced forms of periodontitis may lead to tooth loss in adulthood and subsequently cause high costs for prosthetic rehabilitation. At the age of 35-74 years, approximately 55% of the German population has moderate or severe periodontal disease [1].

Standard care includes mechanical removal of the biofilm, i.e., initial sub- and supragingival mechanical debridement and lifelong supportive periodontal therapy [2, 3]. The outcome of mechanical therapy differs and further disease progression may occur. Patients might benefit from the adjunctive use of systemic antibiotics. An individual patient usually is not infected with all of the above-mentioned pathogens simultaneously, but harbors at least some of these [4]. Due to the differing prevalence of periodontal pathogens, costly and time-consuming microbiological testing is recommended. In half of the periodontal patients the combination of amoxicillin and metronidazole has shown to be an effective antibiotic regime to combat periodontal infections [6, 7].

During the last several years, some controlled clinical trials [8-12] have revealed that the use of this adjunctive antibiotic regimen results in more favorable clinical outcomes, e.g., a greater reduction of the probing depths. In three systematic reviews about the impact of various adjunctive antibiotic agents in periodontal therapy released by the European Federation of Periodontology [5, 13] and the American Academy of Periodontology [14],

methodological weaknesses of existing studies were described. Due to various study designs, small sample sizes, mixed populations, the use of weak endpoints for the determination of disease progression, and the short duration of the studies (weeks to months), definite conclusions about the efficacy of adjunctive antimicrobial therapy have not yet been possible. The conclusion of all reviews was that an adjunctive antimicrobial therapy may affect the clinical periodontal conditions but it is still unclear if any patients and which patients benefit from this adjunctive therapy in general. Therefore, there is a strong need for trials on large patient samples with sufficient observation periods and real endpoints.

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1.1 The ABPARO trial (www. abparo.de)

The present clinical trial was designed and realized with regard to the suggestions made in the above mentioned systematic reviews. Therefore, the trial stands out from others by the sample size, the selection of an objective parameter of disease progression (“attachment loss”, primary outcome parameter), and, besides other clinical parameters, the simultaneous collection of microbiological, genetic, and psychological parameters. Additionally, a true subjective endpoint (“oral health-related quality of life”) was assessed.

The ABPARO-trial was designed as a double-blind, parallel group, randomized, placebo-controlled multi-center efficacy study (phase IV study). Patients with at least ten teeth, with

periodontal screening index of grade IV in at least one sextant, pocket probing depths of ≥ 6 mm at a minimum of four teeth; and age between 18-75 years were included into the trial. The experimental intervention was mechanical debridement plus 500 mg amoxicillin and 400 mg metronidazole three times daily for 7 days, whereas control intervention consisted of mechanical debridement alone. All patients received supportive periodontal therapy in 3-month intervals. The overall duration of intervention was 27.5 months. Our hypothesis was that the administered empiric adjunctive antibiotic therapy would reduce about one half of the proportion of sites with attachment loss compared to subgingival debridement alone (over a 27,5-month period) in a statistical and clinical significant manner. The trial was designed to address the following research questions:

(i) What is the size of the benefit of an adjunctive empiric antibiotic therapy compared to standard mechanical debridement and oral hygiene instructions in a representative sample of German periodontitis patients?

(ii) Does the administration of the antibiotic therapy delay recurrence of periodontitis in the general population and in specific high risk groups (e.g. smokers) under standard supportive therapy?

(iii) Is the presence of specific microbial complexes a useful predictor of outcome and recurrence of periodontitis?

(iv) Does the administration of the antibiotic therapy affect the oral health related quality of life?

The primary endpoint serves the percentage of sites showing attachment loss ≥ 1.3 mm over a 27.5-months period. As secondary endpoints, the subjective perception of treatment outcome, attachment gain, pocket probing depths, bleeding on probing, full mouth plaque score, and the microbial colonization dynamic were examined. Additionally, venous blood samples and patient DNA was sampled.

It was proposed that five hundred patients will be recruited in this twelve-visit trial. The participating patients were stratified for extent of periodontal disease and smoking habit (non-/light smoker: less than 7 ppm CO in exhaled air; moderate to heavy smoker: equal to or more than 7 ppm). Four strata were foreseen (i) non-/light smokers with < 38% of teeth with pocket probing depths ≥ 6 mm, (ii) non-/light smokers with ≥ 38% of teeth with pocket probing depths ≥ 6 mm, (iii) smokers with < 38% of teeth with pocket probing depths ≥ 6 mm, and (iv) smokers with ≥ 38% of teeth with pocket probing depths ≥ 6 mm. Randomization were done according to a prepared randomization list. Test and control group patients receive the same standard periodontal therapy (mechanical supra- and subgingival debridement in two sessions on two consecutive days), except for administration of an adjunctive antibiotic therapy (test) or a placebo drug (control) for seven days at visit 3. The medications are

prescribed directly after finishing mechanical debridement. The coordinating center for this multi-center trial is the Department of Periodontology, University of Münster, Germany. The other participating sites are the Departments of Periodontology of the Universities of Berlin, Dresden, Frankfurt, Gießen, Greifswald, Heidelberg, and Würzburg. Management support, including SAE management, is provided by the "Zentrum für Klinische Studien" Münster (ZKS Münster), University of Münster. Biostatistics already was (i.e. power analysis) and will be conducted centralized in the Institute of Biostatistics and Clinical Research, University of Münster

The trial was conducted according to the ICH/GCP E6 guidelines, and was approved by the Ethic committee of the Medical Association Westfalen-Lippe (ethic committee No: 2006-474-f-A) and the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM Vorlagenummer: 4033777). Additionally, the trial is registered (EudraCT No: 2006-005854-61, ISRCTN No: 64254080). The clinical trial period was public funded by the "Deutsche Forschungsgemeinschaft (DFG)" (DFG No.: EH 365/1-1).

2. Current state of the ABPARO project

A power analysis, prepared in the run up of the study, revealed that a minimum of 350 patients are needed (175 each group). The recruitment of subjects for this trial started in October 2008 and was completed in October 2009. Overall, 3261 patients were screened for eligibility and 542 patients were included into the trail. The last patient completed the 27.5 months intervention and follow-up period at the end of December 2011. In the end 405 patients finished the trial. Up to now, the responsible biometrician, together with the staff of the ZKS Münster, is engaged in finalizing data bank queries and performing initial plausibility testing. The data bank will be closed in the middle of April 2012, and a preliminary biometric analysis will be prepared. These preliminary results will be presented on the EFP meeting in the beginning of June 2012 in Vienna, Austria.

The trial was initially funded by the Deutsche Forschungsgemeinschaft (DFG). Funding was directed primarily to clinical project realization. The DFG funded biometric work focused on initial power analysis, sample size calculation, and, after finalizing the data bank and plausibility testing, preparing a primarily analysis for the first results. Thereafter, the DFG-funding will end and no prolongation is possible due to the bylaws of the funding program. During the project a large amount of data was collected, and there is a strong need for an ongoing biometric support to analyze the entire ABPARO data in an adequate way. Therefore, it is very important for the trial that the biometric support continues. The amount of patients completed the study and the extensive documentation of clinical, microbiological,

psychological, and laboratory parameters offers the possibility of detailed sub-analyses. In due consideration of these parameters, the expected results should be generalizable to a population level. Furthermore, the data allow developing a risk model for long-term disease progression and prognosis in patients suffering from periodontal disease

2.4. Research Questions

In the following, the main general research questions to be addressed in the next two years are listed:

"What is the size of the benefit of an adjunctive empiric antibiotic therapy compared to standard mechanical debridement in a representative sample of German periodontitis patients?"

Primary outcome is the frequency (%) of sites showing changes in clinical attachment level (loss or gain) ≥ 1.3 mm from V2 /V4 (both baseline measurements) through V12 (test compared to control group). First, mean values should be calculated. In a further analysis, the frequency of gain or loss of clinical attachment ≥ 1.3 mm will be calculated with respect to the initial pocket probing depth (sites depths at V2 and V4 of 0-3 mm, 4-6, and >6 mm). If there will be no differences at V12, analysis will be altered to detect possible differences at visits V6, V8, V10, and V12). These calculations will be repeated with different thresholds for attachment gain/loss (1.3 mm, 2 mm and 3 mm). Analysis also differentiates between active and non-smokers and initial disease severity according to initial stratification.

"Is the presence of specific microbial complexes a usefully criteria for selection of antibiotics and a predictor of treatment outcome and recurrence of periodontitis?"

This project is about the question if specific antibiotic regimes are more effective in periodontology than rationale antibiotic regimes. This will have a strong impact on microbiological testing frequency in periodontology in future.

In the trial we used am empiric antibiotic regime without consideration of the composition of the subgingival microflora. In a preliminary study, it was shown that approximately half of our test group patients would be treated specifically with amoxicillin and metronidazole, whereas the other half was treated non-specific. With the parameters attachment level change (% of sites showing attachment gain or loss 1.3 mm, 2 mm, or 3 mm from V2/V4 through V12), changes in the proportion of pocket probing depths (0-3 mm, 4-6 mm, and >6 mm), and the absolute changes in attachment level, we will compare the treatment outcomes between specific and non-specific treated patients. Additionally, after patients will be grouped with

respect to their subgingival microbiological composition, also comparisons between test and control group patients will be analysed.

"Clinical effects after adjunctive systemic amoxicillin and metronidazole or mechanical debridement alone in patients harboring subgingival *Aggregatibacter actinomycetemcomitans* and/ or *Porphyromonas gingivalis*."

In this sub-analysis, the efficacy of the antibiotic regime in patients initially harboring or not *A.a.* and or *P.g.* will be compared. As primary outcomes variables will serve the absolute values (mm) of attachment gain/loss, changes in mean pocket probing depth (PPD), and other surrogates. Additionally the frequency (%) in PPD and attachment level changes (gain/loss 1.3 mm, 2 mm, and 3 mm; at sites showing initially PPD 0-3 mm, 4-6 mm, and >6 mm) will be analysed.

"Does the administration of the antibiotic therapy affect the oral health related quality of life?"

This part on analyses focus on the in the study used five psychological questionnaires. The questionnaire package included the Perceived Stress Questionnaire (PSQ), Hospital Anxiety and Depression Scale (HADS-D), Oral Health Impact Profile – German Version (OHIP-G 49), for assessment of the burden of disease the Short-Form health survey (SF-36), Client Satisfaction Questionnaire (CQS), and the Psychosocial Impact of Dental Aesthetics Questionnaire (PIDAQ). The questionnaires (grade scale) will be analysed first for inter-group differences at baseline and V12, and in a second step, the psychological results will be correlated to clinical-dental results (i.e. changes in attachment level [mm] and pocket probing depth [mm]) and microbiological parameters (prevalence %). Furthermore, results of the questionnaires will be correlated to tooth loss. Analyses will be done at first V2 compared to V12 results, additionally changes during the course of the study will be analysed (V2 through V12).

"The impact of oral hygiene instruction and supragingival scaling on the attachment level gain/loss and on changes in pocket probing depths in patients with moderate to severe chronic periodontitis after mechanical debridement alone or with adjunctive antimicrobial therapy."

Outcome variables are changes in attachment level (frequency [%] of gain/loss using thresholds of 1.3 mm, 2 mm, and 3 mm) and changes in pocket probing depths (mm). Analyses compare these parameters in relation to the complexity of pre-therapy oral hygiene

instructions and frequency of supragingival scaling visits scores and in relation to group assignment (V2 through V12 and V4 through V12).

“Necessity for surgical interventions in test and control group in a baseline to 27.5 months comparison”

As outcome variable will serve the remaining frequency (%) of pocket probing depth of 5 mm or more in test or control group (V2 and V4 through V12). Sub-analyses will be done regarding initial stratification.

“The impact of adjunctive antimicrobial therapy on bleeding on probing (BOP) and supragingival plaque scores (PI) after test and control treatment.”

For this project, as primary variable will serve the differences in the change of total BOP and PI scores during the course of the study (V2 through V12) in test and control group patients.

“The impact of oral hygiene instruction and supragingival scaling on plaque and bleeding scores following therapy in patients with moderate to severe chronic periodontitis.”

Outcome variables are the total plaque and bleeding on probing scores. Analyses compare these parameters in relation to the complexity of pre-therapy oral hygiene instructions and frequency of supragingival scaling visits scores and in relation to group assignment (V2 through V12 and V4 through V12).

“Analyses about clinical and radiographic changes in furcation involved teeth.”

This part is about comparisons of therapy outcomes in test and control group patients on furcation-involved teeth (V2 through V12 and V4 through V12). Furcation involvement is one of the most important known risk factors for tooth survival. In a sub-analysis, results of conventional clinical and radiographic examinations will be compared to the finding of digital volume tomography (DVT) performed in a sub-sample at the center in Würzburg. Primary outcome are the grade and its change through the trial period of furcation involvement detected during clinical and radiographic examinations. Further comparison will answer the question whether or not addition radiographic diagnostics (DVT) will have a clinical significant effect on treatment decisions in future.

“The comparison of different dosage of amoxicillin and metronidazole on clinical parameters and therapy outcome”

Frequency of side effects after antibiotic dosage according ABPARO protocol compared to the original dosage described by van Winkelhoff in 1994. For comparison will serve an external control group from the center in Würzburg. As outcome parameters will serve the changes in absolute pocket probing depths (mm) and attachment level (mm).

“How long must we wait to measure the maximum of benefit after adjunctive antimicrobial therapy or debridement alone, regarding decision making and prognosis?”

This addresses the question after which period of time no further clinical or microbiological improvement after test and control treatment is expectable. Parameters are the change in the percentage of periodontal pockets ≥ 5 mm (%), and the changes in bleeding on probing especially in teeth with initial probing depths ≥8 mm.

“Does the positive detection of *Aggregatibacter actinomycetemcomitans* and/or *Porphyromonas gingivalis* predict the incidence of cardio-vascular events?”

This sub-analysis evaluates, if the incidence of cardio-vascular events in the patient sample is correlated with the subgingival prevalence of *A. actinomycetemcomitans* and/or *P. gingivalis*, and if the mode of therapy has an influence on this incidence.

“The short and long-term effects of different periodontal therapies on changes of pulse wave velocity?”

This sub-analysis will evaluate the impact of periodontal therapy with or without adjunctive antibiotics on the alteration of the pulse wave velocity in periodontal patients.

“Which patients are predestined for suffering from fever and shivering fit after periodontal therapy?”

This analyses will evaluate the incidence of shivering fit after periodontal therapy, and compares the incidences in a group comparison. Clinical and other parameters are tested for correlation, and predisposing factors for this event should be identified.

"Is the HbA_{1c} parameter a positive predictor for insufficient therapy results and further disease progression?

This analysis evaluates the impact of different HbA1c levels after mechanical debridement with or without adjunctive antibiotic therapy on disease progression (attachment loss in thresholds 1.3mm, 2mm, and 3mm) as well as the amount of pocket probing depth reduction.

"What is the impact of the presence of initially severe gingivitis on periodontal therapy results?"

Gingivitis possibly influences the periodontal therapy outcome. However, due to this dogma, elaborative efforts against gingivitis are performed prior periodontitis therapy. Outcome parameters are attachment loss/gain (mm), bleeding on probing (%), changes in pocket probing depths (mm), and the patients' subjective perception of the treatment outcome (questionnaire index).

"Will periodontal therapy change the serum CRP levels and affect the CRP-associated cardiovascular risk?"

This analysis evaluates the initial C-reactive-protein (CRP) level and its change during the observation period. Results will be tested for correlation with clinical results (i.e. pocket probing depth reduction) and, additionally, the alteration in the CRP-associated cardiovascular risk will be monitored.

3. Biostatistical methods and analyses

The collected data will be checked for plausibility. In order to detect measurement errors extreme values of probing parameters e.g. will be identified. Characteristics of the study population, potentially influential parameters, and outcome variables will be described in detail using standard descriptive methods. Categorical data will be presented using frequency and contingency tables. Metric data will be summarized by minimum, maximum, quantiles, mean, standard deviation, and skewness.

According to the intention-to-treat (ITT) principle, the primary efficacy analysis will include all randomized subjects. In addition, a per-protocol analysis will be carried out. In order to determine the efficacy of the treatment effect statistical analyses will be performed on different levels. I.e., the change in parameter values will be assessed in patient-based, tooth-based and site-based analyses. In each of the three approaches appropriate statistical

methods will be applied which account for the different nested data structures and dependencies.

Outcome parameters (cf. 2.4)

- Occurrence of sites with periodontal attachment gain/loss (≥ 1.3 mm, 2 mm and 3 mm) from visit V2/V4 through V12
- Absolut attachment gain/loss from visit V2/V4 through V12
- Changes in pocket probing depths (mm) from visit V2/V4 through V12
- Categorized pocket probing depths (0-3 mm, 4-6 mm, and >6 mm)
- Occurrence of pocket probing depth >= 5 mm in visit V2, V4, … V12
- Changes in supragingival scaling visits scores (visit V2/V4 through V12)
- Grade and change in furcation involvement (visit V2/V4 through V12)
- Occurrence of periodontal bleeding on probing visit V2/V4 through V12
- Grade scale from questionnaires PSQ, HADS-D, OHIP-G 49
- Occurrence of side effects
- Changes in blood parameters (i.e. HbA_{1c}, CRP)
- Changes in psychological parameters

Potentially influential variables

- Antibiotic treatment
- Initial pocket probing depth (sites depths at V2 and V4 of 0-3 mm, 4-6, and >6 mm)
- Active and non-smoking
- Specific and non-specific antibiotic regimes
- Subgingival microbiological composition
- Complexity of pre-therapy oral hygiene instructions and frequency of supragingival scaling visits scores
- Dosage of amoxicillin and metronidazole
- Severity of chronic periodontitis
- Demographic and behavioral factors (i.e. age, body weight, graduation)

Subgroups

- Treatment and control group
- Initial pocket probing depth (sites depths at V2 and V4 of 0-3 mm, 4-6, and >6 mm)
- Active and non-smokers
- Patient treated with specific and non-specific antibiotic regimes

- Patients initially harboring specific microbiological colonization patterns (i.e. identification of *A.a.* and/or *P.g.)*
- Patients with bacteremia
- Patients with/without cardiovascular events
- Blood parameters (i.e. high vs. low CRP levels, pathological vs. physiological blood glucose levels).

The analysis of the primary outcome will be done using confirmative statistical methods. The primary outcome is the proportion of sites showing changes in clinical attachment level (loss or gain ≥ 1.3 mm) from V2 /V4 (both baseline measurements) through V12. This will include the comparison of both randomized groups as a whole using the stratified Wilcoxon test statistic [7]. A two tailed p-value less than 0.05 will be considered as statistically significant. Additional analyses will be performed with respect to the initial pocket probing depth at visit V2/V4 and further thresholds for attachment gain/loss (2 mm and 3 mm).

In exploratory analyses the subgroups above will be compared using univariate statistical methods to detect systematic differences. Correlations between the parameters will be examined. Normally and non-normally distributed data will be analysed with parametric and non-parametric methods, respectively. Point estimates of summary statistics will be supplemented by 95% two-sided confidence intervals. Additionally multivariate statistical analyses will be conducted. The results will be presented separately for each stratum and each study center.

The research questions in 2.4 will be answered with the following statistical methods. The outcome parameters between two visits will be compared with the corresponding statistical two-sample significance tests. For pairwise comparisons of the outcome parameters between two visits and between the subgroups raw p-values and p-values adjusted for multiple testing will be given. Time analyses over all visits from V2/V4 through V12 will be performed using multivariate statistical methods. For each outcome parameter appropriate multivariate models will be established, i.e. in case of binary outcome logistic regression models and in the case of metric outcome parameters general linear mixed models and general estimation equation (GEE) [4, 8]. The adjusted impact of each potentially influential variable on the outcome parameter will be estimated.

Further multivariate analyses will be performed to explore prognostic and predictive factors for forecasting periodontal disease progression and to identify subgroups which benefits most from the therapy. Therefore, all research questions in 2.4 and outcome parameter are put in relation. The prognostic factors and subgroups are determined by demographical, radio graphical, microbiological, genetic, psychological, and clinical data (cf. 2.4). The aim is

to determine a statistical model which describes the periodontal disease progression best, i.e. the change of the percentage of sites with periodontal attachment gain/loss. For each established model, model and variable selection methods will be applied. Sensitivity analyses will be accomplished to determine the quality and validity of the fitted models.

Handling of missing values

a) To assess the different reasons why subjects dropped out (non-responder), a short questionnaire was sent to every non-responder. This questionnaire contained three parts [2]: (i) general reasons for dropout (no time, no interest, etc.), (ii) reasons related to the treatment (side-effects, pain during probing, long duration of the session, etc.), and (iii) reasons related to outcome (side-effects, no improvement, improvement not as expected, etc.).

b) In order to convert a missing not at random (MNAR) situation into a missing at random (MAR) situation [5], each participant was asked at the end of every visit: “Do you think you will be able to attend the next scheduled session?”. The interviewer rated these answers according to the possibility that the patient will attend the next schedule on a 5 point scale (1: "sure", 2: "possible", 3: "unclear", 4: "possible not", 5: "unlikely”). Additionally, reasons for possible drop out of the patient are recorded by the interviewer. This measure supports incomplete data analyses as it counteracts the most important assumption (missing at random).

c) Incomplete data analyses will be performed with and without multiple imputations. Analysis will be based on linear mixed models [8]. The application of multiple imputations is not straightforward and depends on the patterns [6] and on the proportion of missing values [1]. Algorithms for multiple imputations are available in S-Plus and SAS software.

All statistical analyses will be performed by the Institute of Biostatistics and Clinical Research, University of Muenster using standard statistical software packages.

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4. Funding

For successful operation of the proposed projects, we would request for supporting the position of a qualified biometrician. According to the DFG ["Personal Durchschnittssätze der DFG (DFG-Vordruck 60.12-1/08)"] suggestions, the applicants apply for a 50% E14 (TV-L) position for 24 months (66.000€). The position would be located in the Institute of Biostatistics and Clinical Research (University Münster). The holder of the position has unlimited access to the institute's infrastructure facilities, and, therefore, no additional funding of any hard- or software would be necessary. A funding period from June 2012 through May 2014 (24 months) would be suitable. If a complete funding is not possible for the "ARPA-Stiftung", also a partial funding would be very helpful for the successful continuation of the project. For this project no further granting application were applied anywere.

5. Dissemination of results

As mentioned above, first data will be presented in an oral lecture session at the Europerio conference in June 2012 in Vienna, Austria.

The first publication of results will describe the efficacy of systemic antibiotics use in the treatment of periodontal disease (scheduled 2012). Beside the impact on the periodontal status, at first the efficacy of both evaluated therapies will be appraised in terms of the effect on public health and a risk/benefit analysis. We expect that this first result publication may have some axiomatic impact on the future use of systemic antibiotics in periodontology. Therefore, this manuscript will be submitted to an international peer-review medical journal.

Further publications will be submitted to dental medicine peer-review journals. Due to the high overall data quality, we expect a realistic chance to publish these works in international class one dental/periodontal journals (2012-2015). Over all we anticipate approximal 20 original papers from the ABPARO project.

Beside publications in journals, ABPARO results will be presented in lectures and oral presentation. For example, members of the ABPARO consortium are already invited for the ARPA meetings in fall 2012 (Tübingen, Germany) and spring 2013 (Würzburg, Germany). Furthermore, it is scheduled that ABPARO data will be presented in oral and poster presentations at international (IADR/CED Florence 2013, Italy; AAP Philadelphia 2013, USA)

and national (DGP 2013) meetings. Additionally, the national guidelines about antibiotic use in the treatment of periodontitis, as well as the guidelines concerning microbiological diagnostic in periodontal therapy will rephrased according to the results of ABPARO.

Curriculum Vitae

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Employment

Since 08/2008	Managing Director of the Department of Periodontology University Hospital Münster Westfälische Wilhelms University of Münster
06/2005 – 08/2008	Acting head of the Department of Periodontology University Hospital Münster Westfälische Wilhelms University of Münster
03/1999 – 06/2005	assistant dentist at the Department of Periodontology University Hospital Münster Westfälische Wilhelms University of Münster
05/1995 – 02/1999	assistant dentist at the Department of Operative Dentistry and Periodontology University Hospital Würzburg Bayerische-Julius-Maximilians-Universität Münster

Education

2005	Postdoctoral lecture qualification (Habilitation) in Zahn-, Mund- und Kieferheilkunde, Westfälische Wilhems-Universität, Münster.
2003	Appointed to a specialist to Periodontology by the German Society of Periodontology.
2002	Appointed to a specialist for Periodontology by the Dental Association Westfalen-Lippe.
1995	Doctoral thesis in dental Medcine, Bayerische Julius-Maximilians –Universität, Würzburg.
1993	License to practice dentistry.

Research Areas

Clinical studies in the field of non-surgical and surgical periodontal therapy.

Oral microbiology

Relevant Publications (5)

Ehmke B, Moter A, Beikler T, Milian E, Flemmig TF. Adjunctive antimicrobial therapy of periodontitis: long-term effects on disease progression and oral colonization. J Periodontol. 2005 May;76(5):749-59.

Ehmke B, Beikler T, Riep B, Flemmig T, Göbel U, Moter A. Intraoral dissemination of treponemes after periodontal therapy. Clin Oral Investig. 2004 Dec;8(4):219-25.

Ehmke B, Beikler T, Haubitz I, Karch H, Flemmig TF. Multifactorial assessment of predictors for prevention of periodontal disease progression. Clin Oral Investig. 2003 Dec;7(4):217-21.

Rüdiger SG, Ehmke B, Hommens A, Karch H, Flemmig TF. Guided tissue regeneration using a polylactic acid barrier. Part I: Environmental effects on bacterial colonization. J Clin Periodontol. 2003 Jan;30(1):19-25.

Ehmke B, Rüdiger SG, Hommens A, Karch H, Flemmig TF. Guided tissue regeneration using a polylactic acid barrier. J Clin Periodontol. 2003 Apr;30(4):368-74.

External funding received

Total amount 1.629.944 €.

Deutsche Forschungsgemeinschaft (DFG)

2007 Deutsche Forschungsgemeinschaft (DFG), EH 365/1-1
"Adjunctive Antimicrobial Therapy of Periodontitis: Long-Term Effects on Disease Progression and Oral Microbiological Colonization
946.027.00€

Stiftung

2006 Research grant by the „Deutschen Gesellschaft für Parodontologie"
"Patienten- und Site-basierte Risikoanalyse und Prognose von Zahnüberlebensraten bei Parodontitispatienten"
29.000,00€

Dental Association Westfalen-Lippe

2005 Dental Association Westfalen-Lippe, Münster, Germany
"Aufstiegsfortbildung zur Dentalhygienikerin"
74.000,00€

2006 Dental Association Westfalen-Lippe, Münster, Germany
"Aufstiegsfortbildung zur Dentalhygienikerin"
74.000,00€

2008 Dental Association Westfalen-Lippe, Münster, Germany
"Aufstiegsfortbildung zur Dentalhygienikerin"
74.000,00€

2011 Dental Association Westfalen-Lippe, Münster, Germany
"Aufstiegsfortbildung zur Dentalhygienikerin"
74.000,00€

Industrie

1995-1997 Guidor AB, Huddige, Sweden
"*Actinobacillus actinomycetemcomitans* and *Pophyromonas gingivalis* and guided tissue regeneration"
15.385,00€.

2002-2004 Philips Oral Healthcare, Inc. 35301 SE Center Street. Snoqualmie, WA 98065, USA

"Efficacy of sonicare prototype toothbrushing following non-surgical treatment of periodontitis"

195.537,00€

2002-2005 Atrix Laboratories, Fort Collins, Col., USA

"In situ technique using autogenous bone with a 4% doxycycline-containing poly(DL-lactide) barrier in the treatment of intraosseous periodontal defects"

88.000,00€

2011 Dr. Kurt Wolf Pharma Bielefeld, Germany.

"Efficacy of a new carbonate/hydroxyapatite nanocrystal dentifrice on the dental plaque index and the de novo plaque formation rate in individuals suffering from gingivitis and/or periodontitis"

60.000, 00€

Univ.-Prof. Dr. med. dent. Benjamin Ehmke

Curriculum Vitae

Prof. Dr. Dr. Andreas Faldum

Biostatistican

Albert-Schweitzer-Campus 1, A11
48149 Münster, Germany
☎0251 83 50660
faldum.andreas@ukmuenster.de

Date of Birth: March 21st 1961
Place of Birth: Gießen, Germany

Employment

Since 12/2010	Managing Director of the Institute of Biostatistics and Clinical Research Scientific director and chairman of the board of the Centre for Clinical Trials Münster Westfälische Wilhelms University of Münster
10/2008 – 11/2010	Head of the Department of Biostatistics at the Institute of Medical Biostatistics, Epidemiology, and Informatics, University Medical Center of the Johannes Gutenberg-University Mainz
11/1998 – 09/2008	Research associate at the Department of Biostatistics at the Institute of Medical Biostatistics, Epidemiology, and Informatics, University Medical Center of the Johannes Gutenberg-University Mainz
01/1997 - 10/1998	Assistant physician and coordinator of a Picture Archiving and Communication System (PACS) at the Institute of Diagnostic and Interventional Radiology,

	University hospital of Jena
04/1996 - 12/1996	Research associate at the Institute of Mathematics Otto-von-Guericke University of Magdeburg
11/1995 - 12/1995	Research associate at the Institute of Mathematics Johannes Gutenberg-University of Mainz

Education

2008	Postdoctoral lecture qualification (Habilitation) in Biostatistics, Epidemiology and Informatics, Johannes Gutenberg-University Mainz
2006	Degree Medical Informatics
1997	PhD graduation in Mathematics (Dr. rer. nat.), University of Magdeburg
1993	Diploma in Mathematics, University of Mainz
1987	License to practice medicine

Research Areas

Biostatistical consulting of multinational trials in pediatric oncology and hematology

Statistical methods for trials with small sample size or long study duration

Flexible adaptive-sequential study designs

Trustworthiness of data transfer in health research networks

Professional Memberships

Study committees

HIT/SIOP-PNET, HIT/SIOP-LGG 2004

HIT-HGG

HIT-REZ

NB 2004

DSMB EDNET STI-D

Expert committees

Statistics Subcommittee of the International Neuroblastoma Risk Group

Relevant Publications (5)

1. Oberthuer A, Hero B, Berthold F, Juraeva D, Faldum A, Kahlert Y, Asgharzadeh S, Seeger R, Scaruffi P, Tonini GP, Janoueix-Lerosey I, Delattre O, Schleiermacher G, Vandesompele J, Vermeulen J, Speleman F, Noguera R, Piqueras M, Bénard J, Valent A, Avigad S, Yaniv I, Weber A, Christiansen H, Grundy RG, Schardt K, Schwab M, Eils R, Warnat P, Kaderali L, Simon T, Decarolis B, Theissen J, Westermann F, Brors B, Fischer M. Prognostic impact of gene expression-based classification for neuroblastoma. J Clin Oncol. 28(21): 3506-3515, 2010.

2. Götte H, Hommel G, Faldum A. Adaptive designs with correlated test statistics. Stat Med. 28(10): 1429-1444, 2009.

3. Cohn SL, Pearson AD, London WB, Monclair T, Ambros PF, Brodeur GM, Faldum A, Hero B, Iehara T, Machin D, Mosseri V, Simon T, Garaventa A, Castel V, Matthay KK; INRG Task Force. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. J Clin Oncol. 27(2): 289-297, 2009.

4. Faldum A, Hommel G. Strategies for including patients recruited during interim analysis of clinical trials. J Biopharm Stat. 17(6): 1211–1225, 2007.

5. Faldum A. On the trustworthiness of error-correcting codes. IEEE T Inform Theory. 53(12): 4777-4784, 2007.

Eingeworbene Drittmittel
Die Gesamtsumme beträgt 6.515.673 Euro.

Projekttitel	Kooperationspartner (genaue Angaben siehe „Forschungskooperationen“)	Drittmittelgeber	Förderzeitraum	Drittmittelhöhe
Zentrale biometrische Betreuung klinischer Studien der Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH) zur Behandlung von Kindern mit Hirntumoren: - HIT/SIOP-PNET - HIT-HGG - HIT-LGG - HIT-ENDO/	Prof. Dr. S. Rutkowski, Hamburg Dr. F. Deinlein, Würzburg Dr. B. Lannering, Göteborg, Schweden Prof. Dr. R. Kortmann, Leipzig Dr. B. Pizer, Liverpool, UK Dr. F. Doz, Paris, Frankreich PD Dr. C. Kramm, Halle Dr. A. K. Gnekow, Augsburg Prof. Dr. H. Müller,	Deutsche Kinderkrebsstiftung	1. Förderperiode: 15.10.2001 – 14.10.2003 2. Förderperiode: 15.10.2003 – 14.10.2005 3. Förderperiode: 15.10.2005 – 14.10.2008 4. Förderperiode: 15.10.2008 – 14.10.2011 5. Förderperiode: 15.10.2011 – 14.10.2014	273.840 Euro 169.250 Euro 271.500 Euro 305.500 Euro 329.500 Euro

Kraniopharyngeom - HIT-REZ	Oldenburg Prof. Dr. G. Fleischhack, Essen			
Biometrische Betreuung der internationalen Studie SIOP-LGG 2004 zur Behandlung von Kindern mit Gliomen niedriger Malignitätsgrade	Dr. A. K. Gnekow, Augsburg Prof. Dr. O. Witt Heidelberg PD Dr. P. Hernáiz Driever, Berlin Prof. Dr. G. Perilongo, Padua, Italien Dr. D. A. Walker, Nottingham, UK Dr. J. Grill, Villejuif, Frankreich	Deutsche Kinderkrebsstiftung	1. Förderperiode: 01.06.2004 – 30.06.2007 2. Förderperiode: 01.07.2007 – 30.06.2010 3. Förderperiode: 01.01.2011 – 31.12.2013	99.650 Euro 89.630 Euro 86.630 Euro
Biometrische Betreuung der Studie GPOH-MET zur Behandlung maligner endokriner Tumoren im Kindes- und Jugendalter	Prof. Dr. P. Bucsky, Lübeck	Studienzentrale an der Klinik für Kinder- und Jugendmedizin der Universität zu Lübeck	15.06.2004 – 14.06.2005	24.000 Euro
Biometrische Betreuung der multizentrischen Therapieoptimierungsstudie zur Behandlung der schweren aplastischen Anämie im Kindesalter SAA	Prof. Dr. M. Führer, München	Klinikum der Universität München - Innenstadt, Kinderklinik und Poliklinik im Dr. von Haunerschen Kinderspital	20.11.2004 – 19.08.2009	95.000 Euro
Biometrisches Gutachten	Dr. T. Wittig (Medical Director), Hohenlockstadt	Pohl-Boskamp GmbH & Co. KG, Abteilung Medizin	2005	13.000 Euro
Untersuchungen von	Antragsteller:	Deutsche Forschungsgemeinsch	01.06.2006 –	1 TV-L E13 Mitarbeiterstell

adaptiv-sequentiellen Studiendesigns unter Berücksichtigung von Anforderungen aus der klinischen Praxis	Prof. Dr. G. Hommel, Dr. A. Faldum, Mainz	aft (DFG)	31.05.2009	e sowie 5.500 Euro Sachmittel zusammen ca. 160.000 Euro
Biometrische Betreuung der multizentrischen Studie zur risikoadaptierten Behandlung von Kindern mit einem Neuroblastom NB 2004	Prof. Dr. F. Berthold, Dr. B. Hero, Prof. Dr. T. Simon, Köln	Deutsche Krebshilfe	01.03.2007 – 29.02.2016	72.520 Euro
Prospective randomised multicentre trial investigating liver preservation with HTK by simple aortic perfusion in comparison to aortic perfusion plus ex situ arterial flushing	Prof. Dr. G. Otto, Dr. K. Kronfeld Mainz	DFG/Bundesministerium für Bildung und Forschung (BMBF) Förderprogramm Klinische Studien	01.01.2008 – 01.11.2010	43.260 Euro
Prognostic and predictive validation of molecular markers in childhood medulloblastoma	Prof. Dr. S. Rutkowski, Hamburg Dr. S. Pfister, Prof. Dr. P. Lichter, Heidelberg Dr. R. Kläs, Dr. F. W. Cremer, Mannheim Prof. Dr. G. Reifenberger, Dr. J. Felsberg, Düsseldorf Prof. Dr. T. Pietsch, Bonn	BMBF Gesundheitsforschung: Forschung für den Menschen – Molekulare Diagnostik	01.02.2010 – 31.01.2013	41.650 Euro

Prospektive neuropsychologische Untersuchungen bei Kindern unter 4 Jahren mit Medulloblastom / Ependymom im Rahmen der Therapieoptimierungsstudie HIT 2000	Dr. H. Ottensmeier, Würzburg Prof. Dr. S. Rutkowski, Hamburg	Universitätsklinikum Würzburg	01.01.2011 – 31.12.2011	15.000 Euro
Neuropsychologische Nachuntersuchung von Kindern mit einem Alter unter 3 Jahren bei Erkrankung an einem Medulloblastom - Untersuchung 10 Jahre nach Ende der Behandlung	Dr. H. Ottensmeier, Würzburg Prof. Dr. S. Rutkowski, Hamburg	Universitätsklinikum Würzburg	01.01.2011 – 31.12.2011	15.000 Euro
Empirische Analyse der Darmkarzinombehandlung	AOK Nordwest, Mc Kinsey & Company, Inc.	Krebsgesellschaft Nordrhein-Westfalen e.V.	01.08.2011 – 31.01.2012	17.000 Euro
Förderung eines klinischen Studienzentrums an der Medizinischen Fakultät der Westfälischen Wilhelms-Universität Münster Förderkennzeichen: 01KN1105	WWU/UKM Münster	BMBF	01.07.2011 – 30.06.2015	4.393.743 Euro

(Univ.-Prof. Dr. rer. nat. et med. habil. Andreas Faldum)