Final Report – Clinical Trials Programme

1. General information

1.1. Applicant/Coordinating investigator

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53113 Bonn

1.2. Title of trial

Endurance orientated training program with children and adolescents on maintenance hemodialysis to enhance dialysis efficacy - DiaSport

1.3. DFG project number of the original proposal

HO/1272/21-1

1.1. Trial time flow

First patient in:	01.09.2012
Last patient in:	22.04.2016
Last patient out:	30.11.2016
Final report:	23.03.2018

2. Trial design aspects and statistical analysis

2.1. Trial design

Condition	Intervention	Phase
End stage renal disease	**Bicycle Ergometer Training**	**N/A**

To assess the effect of continuous physical training on hemodialysis efficacy in children and adolescents with end stage renal failure and maintenance hemodialysis treatment.

Study type: Interventional
Study design: parallel assignment, open label, randomized, efficacy study

2.1.1. Control(s)/Comparator(s)

Experimental intervention / index test:
Three times weekly bicycle-ergometer training during hemodialysis up to 50 to 70 minutes (warm up, endurance training, cool down) duration and with 70-80% of the patient specific maximum workload during 12 weeks (period 1).

Control intervention / reference test:

Waiting control group: No ergometer training during the first 12 weeks (period 1), then training during the next 12 weeks (period 2).

Follow-up per patient:
none

Duration of intervention per patient:
Group I (Intervention group): 12 weeks intervention (36 training sessions)
+ 12 weeks prolongation (36 training sessions)

Group II (Waiting Control Group): 12 weeks as waiting control without specific training
+ 12 weeks (36 training sessions) as active intervention.

Experimental and / or control off label or on label in Germany:
Not applicable.

2.1.2. Dose, mode and scheme of intervention

Trial period 1:

Group I: At baseline visit (V0) group I starts the performance adapted, hence individualised three times weekly bicycle-ergometer training during hemodialysis. The training lasts 50 up to 70 minutes each and with 70-80% of the patient specific maximum workload over 12 weeks (36 training sessions).

Group II: After baseline visit (V0) group II does not receive any specific training during hemodialysis within the next 12 weeks until visit 1 (V1).

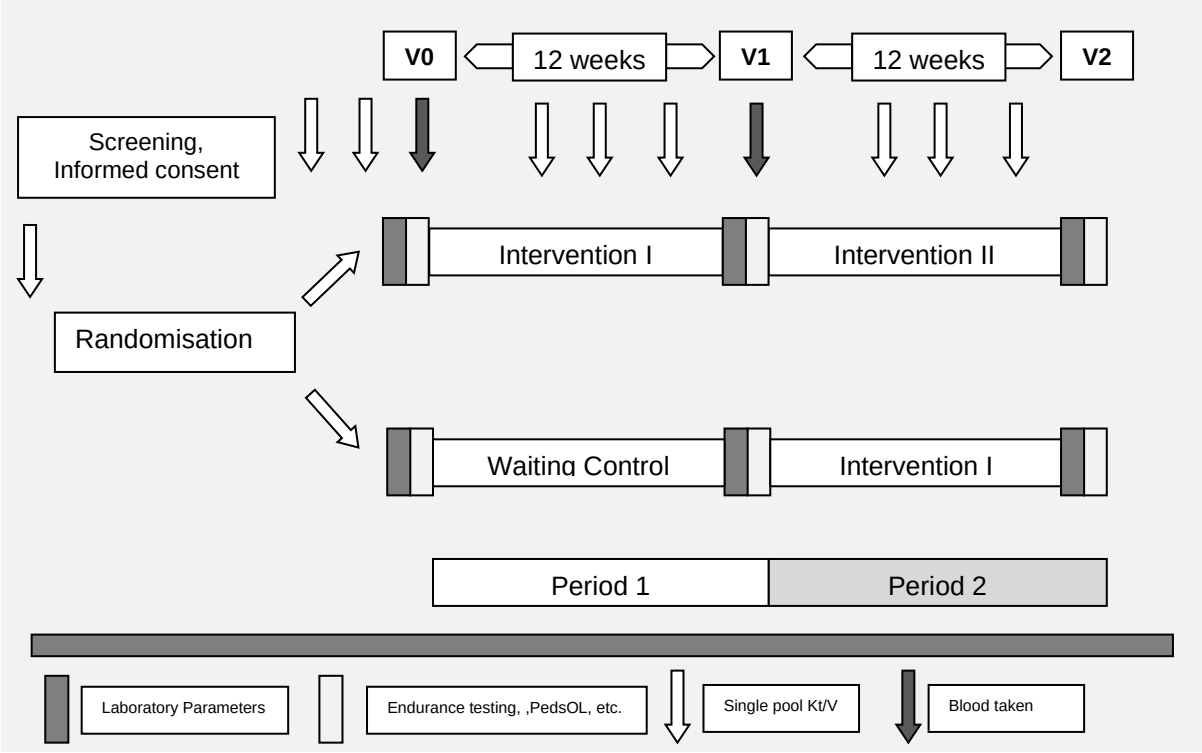
Trial period 2:

Group I: After visit 1 (V1) the again performance adapted training intervention in Group I is prolonged by an additional 12 weeks (36 sessions) training program (intervention II), equal to the program in period 1. This additional training is set to gain information on maintenance of intervention effects.

Group II: The individualised, performance adapted three times weekly bicycle-ergometer training program over 12 weeks (36 sessions) starts after visit 1 (V1).

For all training sessions, an individual training scheme is designed based on the endurance testing scheduled at the study visits. During the training sessions the participants are supervised and monitored by a well-trained assistant student. Furthermore the trial sports scientist is monitoring the interventions by repeated random inspections.

It was planned that after the study completion, all patients should have the possibility to remain on bicycle ergometer training during dialysis as a first step to integrate ergometer training in the standard care of patients on maintenance hemodialysis.



2.1.3. Additional treatments

All patients are receiving hemodialysis treatment, adapted to the patient's medical needs, (at least 4 hours each, three times weekly) according to the practise of the local hospital, the standard operation procedures of the German Pediatric Nephrology Association (www.gp-nephrologie.de) and to the Dialysestandard 2006 (*www.nephrologie.de/DIalysestandar2006.pdf*). Of course, patients usually have potassium, phosphate and protein restricted diet, furthermore they typically have a reduced daily fluid intake (residual urine volume + 500 ml per day). Hemodialysis patients usually receive up to 10 different medications, e.g. phosphate binders, antihypertensive medication, anemia treatment (EPO, ferrum), 25(OH) Vitamin D and calcitriol, other vitamin supplements, aspirin, and, in some cases, antibiotic treatment. Some patients remain on immunosuppressive medication after first kidney transplantation was chronically rejected, or need surgery for transplant removal. All these treatments are permitted during the trial, even cardio selective ß-blockers for the treatment of hypertension are allowed, as far as response of heart rate during the endurance testing is noted. For the reason of safety and as the reduction of concomitant medication is one secondary aim of the trial the type and the amount of medication is documented.

2.1.4. Inclusion and exclusion criteria

Key inclusion criteria:

- End stage renal disease with need of renal replacement therapy
- maintenance hemodialysis for at least 3 month,
- children and adolescents aged ≥ 6 to ≤ 19 years at the time of randomization
- Stable dialysis conditions, as determined by serum parameters and single pool Kt/V, for at least 4 weeks prior to intervention
- Informed consent

Key exclusion criteria:

- Participation in another interventional study
- Uncontrolled hypertension or hypotension
- Recurrent, uncontrolled epileptic seizures
- Kind of heart diseases
- Other severe primary or secondary disease known as a contraindication for endurance training
- Already planned medical intervention, for example living donor kidney transplantation or any other surgery within the next 3 months after randomization, which leads to an discontinuation of training for more than 2 weeks

2.1.5. Determination of primary and secondary measures

Primary endpoint:

- Change of single pool Kt/V (KDOQI Guidelines) – expressed as the change of Kt/V from week 0 to 12 of intervention (period 1) [Time Frame: 12 weeks, designated as safety issue: yes]
  Change of single pool Kt/V (spKt/V) measured at week 12 (V1) compared to baseline (V0). Single pool Kt/V is the standard measure to assess dialysis efficacy. As dialysis efficacy is the primary aim of dialysis treatment and the spKt/V is the best way to measure efficacy this figure has an important clinical relevance for the patient.

Secondary endpoints:

- Change of the possible woarkload (maximum physical performance) achieved [Time frame: 12 weeks and 24 weeks, designated safety issue: no]
  The maximal possible workload is determined by an exercise evaluation program with increasing power on a leg bicycle ergometer before a hemodialysis session, measuring the peak oxygen uptake (VO2-peak), heart rate, blood pressure and lactate levels during exercise.

- Quality of life [Time Frame: 12 and 24 weeks, designated as safety issue: no]
  For quality of life assessment the validated and standardized PedsQL questionnaires are filled in by patients and parents

- Change of solute removal during hemodialysis [Time Frame: 12 and 24 weeks, designated as safety issue: yes]
  Solute removal during hemodialysis has a clear impact on the patients' health and well-being, as it reduces sequelae and offers the patient less restrictions on their diet. Both would lead to a better compliance.

- Change of solute removal in the two compartment model (assessed in a subgroup of patients), [Time Frame: 12 and 24 weeks, designated safety issue: yes]
  Solute removal in the two compartment model is only analyzed in patients 12 years of age or older with explicit consent to a second blood drawing 30 minutes after end of a hemodialysis session. It was previously used showing a significant enhancement during exercise, explained by an increase of skeletal muscles perfusion during exercise.

- Inflammation, nutritional status and bone metabolism [Time Frame: 12 weeks and 24 weeks, designated as safety issue: no]
  The nutritional status and bone metabolism are determined as they are important for optimal health and growth or pediatric hemodialysis patients. Evidence is based on studies that showed trends towards a better nutritional status and less chronic inflammation.

- Body Composition Monitoring (BMC) [Time Frame: 12 and 24 weeks, designated as safety issue: no]
  Body composition monitoring is performed to examine further information on nutritional status, overhydration and muscle composition.

- Change of number and dose of medication needed [Time Frame: 12 and 24 weeks, designated as safety issue: no].

Number and dose of medication are recorded, changes are evaluated and data are correlated to e.g. the measured blood pressure (antihypertensive drugs) or hemoglobin levels (EPO or EPO stimulating agents).

- Telomere length and Telomerase activity [Time Frame: 12 and 24 weeks, designated as safety issue: no]
  Telomere length and telomerase activity are used as markers for cell survival, which may be influenced by endurance training.

2.1.6. Methods against bias

Bias is minimized by randomized group allocation stratified by the respective intervention center. As bicycle ergometer training is the intervention of this trial, a blinded randomization is not possible. Trial sites strategies for hemodialysis may differ; therefore the randomization allocation is stratified by the respective trial site. This is carried out using a computer-based randomization list for each participating centre created at the Institute of Medical Statistics, Informatics and Epidemiology (IMSIE) of the University of Cologne. The waiting group design minimizes bias by reducing drop outs in the control group.
The primary outcome measure, the single pool Kt/V, is only based on quantifiable metric and time values. All outcome measures are obtained by experienced clinicians and training coaches. Investigators and sport assistants at all sites undergo standardized instruction for the outcome measures prior to the study. Auditing and monitoring is carried out according to international GCP guidelines by the close cooperation with the IMSIE and the Clinical Trials Center (ZKS) Cologne, which further assure the quality of the study.
As far as possible, outcome measures are blinded until the end of the trial (e.g. central lab values, quality of life). Although blinding is not possible for all outcome measures, the trial adherence is not influenced by the outcome measures, as these are only addressed after trial period 1 (intervention vs. waiting control) has been finished.
Furthermore we assure individualised bicycle ergometer training in all participating centers, due to a close coordination by the trial sport scientists. The sport scientists carry out the standardised performance testing, on which the individualised heart rate based bicycle ergometer training is based. The adherence to the training should be assured by assistant students in the center, who are in close contact with the coordinating sports scientist. As the used bicycle ergometers offer the opportunity to store training data (heart rate and performance data), data is send online to the coordinating scientist as an objective measurement of training compliance.

2.1.7. Proposed sample size/Power calculations

From our experience, we know that the untreated change of single pool Kt/V has very small variability. From our unpublished data, the mean improvement of single pool Kt/V for a group under ergometer training was about 0.20 with an SD of 0.23, yielding a standardized effect of 0.88. Using the error probabilities of α=0.02 (onesided) and β=0.8, the sample size needed to show such an effect would be n = 26 in each group, i.e. 52 in total. A drop-out rate of 20% is expected; therefore, 66 patients would be needed for randomization. According to own recent experiences, we expected a screening failure rate of up to 50%. This made the screening of 132 patients necessary to assess eligibility (mal compliance, disease related problems, transplantation).

2.1.8. Originality and quality of the study

All trial related procedures were carried out according to GCP guidelines. The study was designed in close collaboration with the methodological part of the Clinical Trials Center (ZKS) Cologne (BMBF01KN0706), the Institute for Medical Statistics, Informatics and Epidemiology (IMSIE), the German Sport University Cologne, the Institute of Sports Medicine of the University of Kiel and the pediatric clinical trial unit at the University Hospital Cologne (Klinisches Studienzentrum Pädiatrie, BMBF01KN0706) to assure quality in all aspects of the study.
The principal coordinating investigator and his clinical staff have great experience in clinical trials and are GCP trained. Several clinical trials are run at the site, both with industrial sponsorship or investigator driven.
A special focus is to assure the quality of the supervised bicycle ergometer training and the ergospirometry testing. All training sessions are supervised by a centrally trained assistant student. The central training at the German Sports University is coordinated by an experienced sport scientist

and focusses on observation of the individual training, adherence to the training, motivation, and assessment of adverse events. A training manual addressing these aspects is provided. All physiologic and metabolic testing is carried out by an experienced sports scientist of the German Sport University Cologne according to the trial specific manual. The trial sports scientist supervises the training at the local hospitals by regular telephone calls and inspections at site and by monitoring of the training data documented online by the sites (heart rate, workload achieved). Thus the possibility to exchange experience and to address problems is continuously given.
A selection visit was carried out at each participating center to ensure they have the resources to carry out all trial related activities according to GCP guidelines, are able to recruit sufficient patients, and are willing to supervise the training of the patients according to the trial guidelines (see 4.2. Monitoring).
Monitoring is performed by the ZKS Cologne. The performance of monitoring follows the ADAMON criteria (TMF project "GCP conform monitoring in IITs, http://www.tmfev.de/site/DE/int/AG/MKS/Projekte/IIT-Monitoring/c_Monitoring.php; BMBF 01EZ0876). A monitor inspects the study center regularly to ensure implementation of the study protocol, high quality of documentation, to check the declarations of informed consent, to monitor patient safety, to check the completeness and accuracy of collected patient data and to ensure that the study is conducted in accordance with the study protocol, the principles of GCP and local legislation. In addition to the selection visits, each center was visited for initiation and for closeout. Regular visits are performed throughout the study in the participating centers.
The IT infrastructure and data management is supplied by the ZKS Cologne. The ZKS Cologne uses the electronic trial data systems MACRO for the data entry. MACRO is a validated system with an audit trail, ensuring that only authorized persons will enter data, make additions, or deletions. The use of MACRO allows enforcement of standard operation procedures to confirm the validity of the trial conduct and integrity of data collected. Data is entered online at the trial sites via the Internet. Plausibility checks are run during data entry. The ZKS Cologne Data Management Department is conducting further checks for completeness. All procedures are described in detail in the data management manual. All tasks of ZKS Cologne are performed according to SOPs of ZKS Cologne.

2.2. Statistical Analysis

Efficacy / test accuracy:

Comparison of the changes in single pool Kt/V from week 0 to week 12 between the treatment groups. The primary endpoint will be evaluated by an analysis of covariance with fixed factors treatment group and center and baseline as covariate. For the waiting control group (group II) the changes in period 1 (no intervention) and 2 (training intervention) will be compared by a paired t-test. In group I the second intervention period will be compared to the first by descriptive statistics to assess the effects of prolonged maintenance of training.

Description of the primary efficacy / test accuracy analysis and population:

The primary efficacy analysis is based on a modified intention-to-treat (mITT) population. Patients who drop out because of kidney transplantation will be excluded from this mITT set. Additionally an intention-to-treat (ITT) and a per-protocol (PP) analysis will be performed.

Safety:

Cross tables and listings of adverse events.

Secondary endpoints:

The secondary endpoints will be analyzed by appropriate Ancova models, non-parametric or Chi-Square tests and descriptive statistics.

3. Quality Assurance and Safety

3.1. Declaration of DSMB or TSC

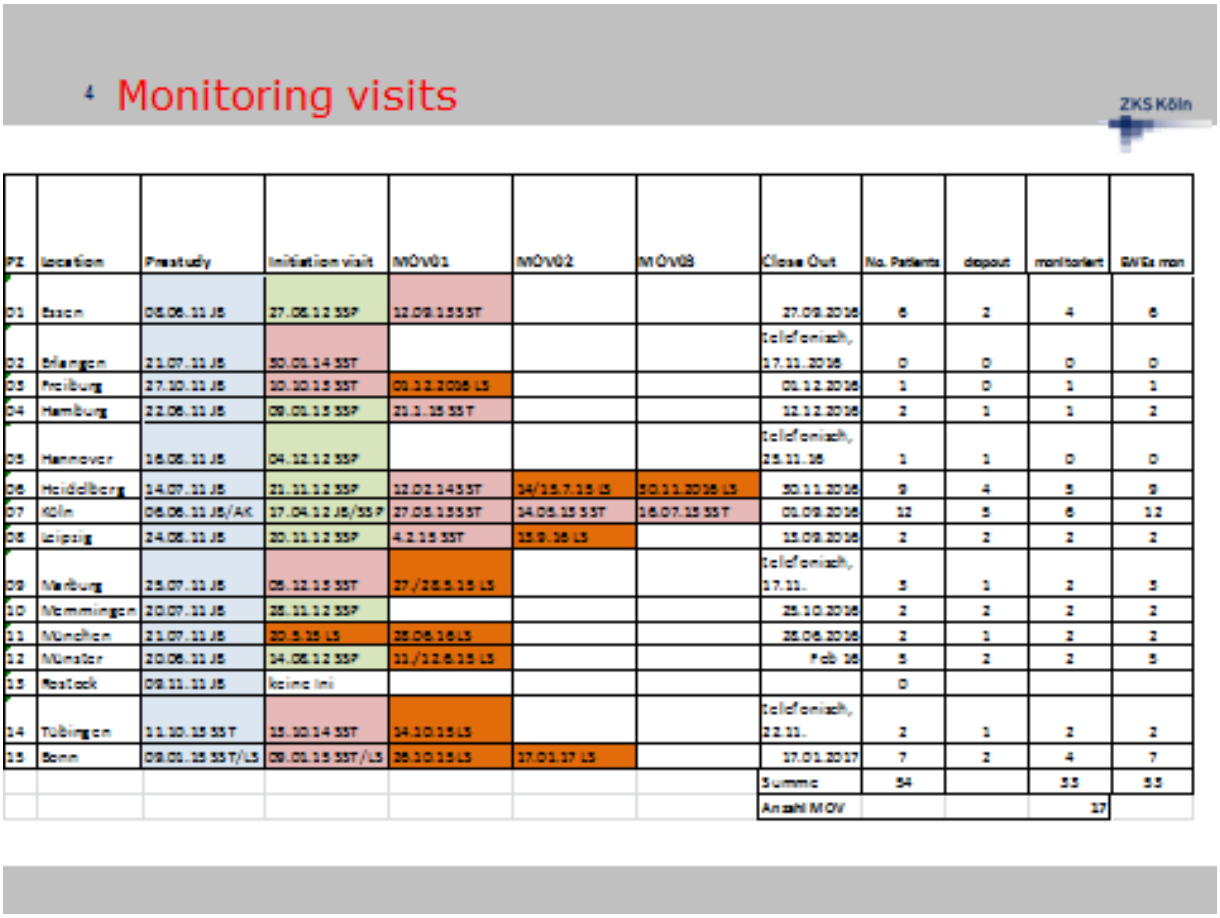
n.a.

3.2. Monitoring

Monitoring visits were performed according to the Monitoring Manual V1-08-F. One pre-study selection visit per site was performed for all of the 15 study sites. One initiation visit per site was performed for 14 study sites (site 14 – Rostock was not initiated). All centers were finally monitored and got a closing monitoring visit.

The principal investigator and his local team investigated all monitoring reports carefully and gave feedback to the centers, if necessary. In addition, all files were interpreted by giving notes of severity of problems. If applicable either the study nurse, or the principal investigator talked with the individual center, or even was visiting the center for clarifications.

In two centers we were unable to install the eCRF to due local data security hazards. Here, we printed all eCRF files out, which were filled out and signed by the local PI and the study nurse in Bonn then entered the data according to the written documents into the eCRF system.



PZ	Location	Prestudy	Initiation visit	MÖV01	MÖV02	MÖV03	Close Out	No. Patients	dapout	monitoriert	BWSs mon
01	Essen	05.06.11 JS	27.06.12 SSP	12.08.13 SST			27.09.2016	6	2	4	6
02	Erlangen	21.07.11 JS	30.01.14 SST				telefonisch, 17.11.2016	0	0	0	0
03	Freiburg	27.10.11 JS	10.10.13 SST	01.12.2008 LS			01.12.2016	1	0	1	1
04	Hamburg	22.06.11 JS	09.01.13 SSP	21.1.15 SST			12.12.2016	2	1	1	2
05	Hannover	16.06.11 JS	04.12.12 SSP				telefonisch, 25.11.16	1	1	0	0
06	Heidelberg	14.07.11 JS	21.11.12 SSP	12.02.14 SST	14/15.7.15 LS	30.11.2016 LS	30.11.2016	9	4	5	9
07	Köln	06.06.11 JS/AK	17.04.12 JS/SSP	27.08.13 SST	14.08.15 SST	16.07.15 SST	01.09.2016	12	5	6	12
08	Leipzig	24.06.11 JS	20.11.12 SSP	4.2.15 SST	15.9.16 LS		15.09.2016	2	2	2	2
09	Marburg	25.07.11 JS	05.12.13 SST	27./28.5.15 LS			telefonisch, 17.11.	3	1	2	3
10	Memmingen	20.07.11 JS	28.11.12 SSP				28.10.2016	2	2	2	2
11	München	21.07.11 JS	20.5.15 LS	28.06.16 LS			28.06.2016	2	1	2	2
12	Münster	20.06.11 JS	14.06.12 SSP	11./12.6.15 LS			Feb 16	3	2	2	3
13	Rostock	09.11.11 JS	keine Ini					0			
14	Tübingen	11.10.13 SST	15.10.14 SST	14.10.15 LS			telefonisch, 22.11.	2	1	2	2
15	Bonn	09.01.13 SST/LS	09.01.13 SST/LS	26.10.15 LS	17.01.17 LS		17.01.2017	7	2	4	7
							Summe	54		53	53
							Anzahl MOV			17	

4. Final Status report

4.1. Milestones

4.1.1. Trial registration (date, trial number, database)

20.3.2012, NCT01561118, Clinical trial gov

4.1.2. Trial protocol (date, version)

Trial protocol version 2.1. – 2. Amendment, dated 25.4.2015

4.1.3. Protocol publication (date, title, database)

The trial protocol is not published, but only provided to the participating hospitals

4.1.4. Ethics vote (date of original ethics vote and amendments)

- 07.03.2012 positive ethics vote University of Cologne (primary sponsor of the study)
- 14.08.2012 positive ethics vote UK Cologne for editorial changes submitted in 07/2012
- 06.08.2013 positive vote of UK Cologne for change to UK Bonn as primary sponsor
- 04.09.2013 positive ethics vote UK Bonn
- 04.05.2015 positive ethics vote of UK Bonn for amendmend 2 (upddated study protocoll, ICF and information brochure, version 2.1. [25.04.2015])

4.1.5. First patient in (date)

ICF at 13.08.2012 and randomization at 11.09.2012

4.1.6. Total amount of patients in (number and percentage)

54/66 (82 %)

4.1.7. Last patient in (date)

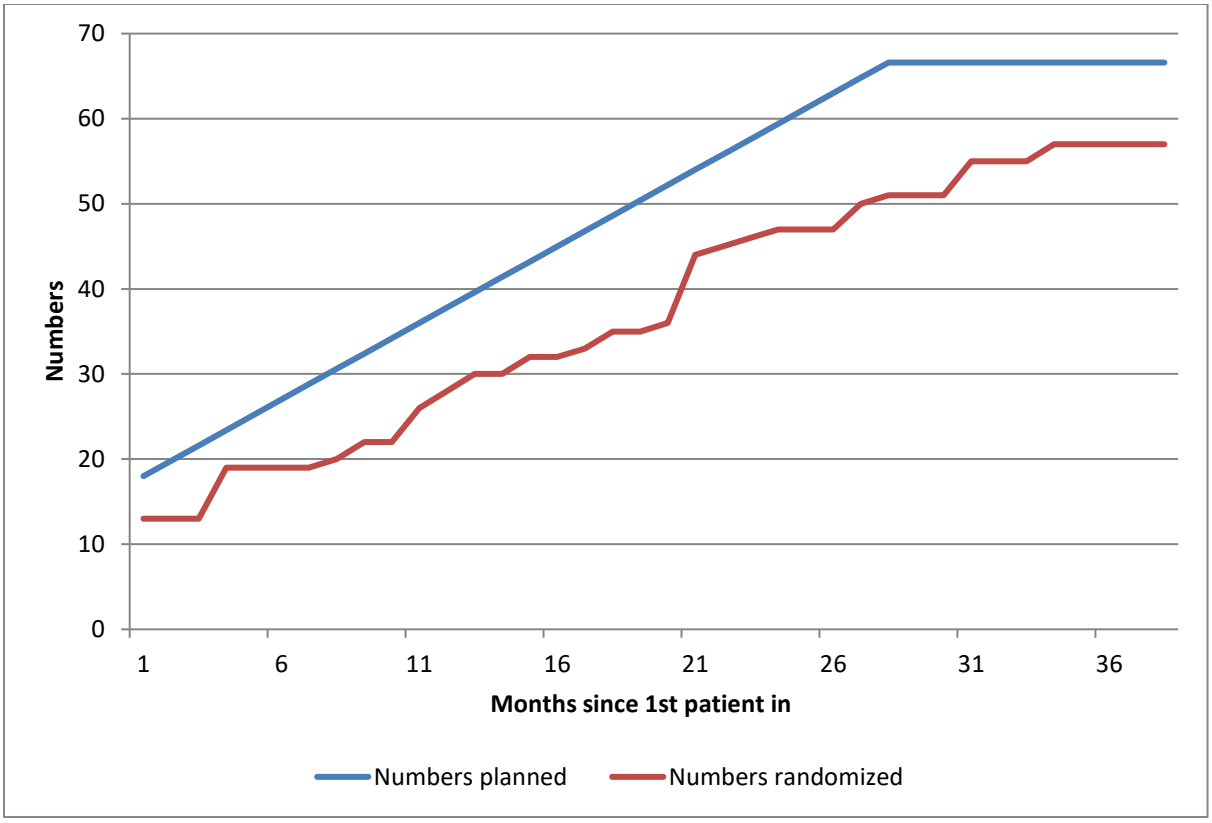
22.04.2016

4.1.8. Last patient out (date)

30.11.2016

4.2. Recruitment

4.2.1. Recruitment graph



The zero timepoint of the recruitment plan was set to time of "1st patient in" in 09/2012

4.2.2. Recruitment/Screening table

Center-No.	Town	Patients final
1	Essen	6
2	Erlangen	
3	Freiburg	2
4	Hamburg	2
5	Hannover	
6	Heidelberg	9
7	Köln	15
8	Leipzig	2
9	Marburg	3
10	Memmingen	1
11	München	2
12	Münster	5
13	Rostock	Not initiated
14	Tübingen	2
15	Bonn	8
Overall		57

4.2.3. Recruitment problems

There were more than some recruitment problems over the first two years of the study. Most ot the problems appeared because patients either received a kidney transplant, or were included in competing studies. For example, in Hamburg, most of the patients were transplantated and hence, there was a big discrepancy between previously planned and finally included patients.

As the recruitment problems went further, we opened up two previously not planned centers (Türbingen and Bonn) and we finally decided to only include new patients from our own center into the study. There were two more patients in Hamburg, but due to the change of the division head, we were not able to include those patients in time. From all other centers we got negative answers (mid to end of 2016), except from Tübingen (n=1), but we had then already decided to stop recruitment (see explanation below).

Center	Planned	N included
Essen	4	6
Erlangen	4	0
Freiburg	1-2	1
Hamburg	16	2
Hannover	8	1
Heidelberg	4	9
Köln	14	12
Leipzig	10	2
Marburg	2	3
Memmingen	2	2
München	4	2
Münster	3-6	5
Rostock	1-2	0
Tübingen	-	2
Bonn	-	7
Summe	**71-76**	**54**

4.2.4. Improvement of patient recruitment

The only true improvement was the opening of our own center for patient recruitment, so that we could include all our recent patients into the study.

4.2.5. Conclusion

We were not able to include all 66 patients into the study and finally had to decide to close doors for recruitment, as we had to acknowledge decline of interest (competing studies with more coverage per patient were started in the meantime), but also because of a lack of money. Hence, after discussing matters in the team, but especially with the statistician, we decided to stop recruitment also for the sake of getting appropriate evaluation of results in due time.

5. Final results

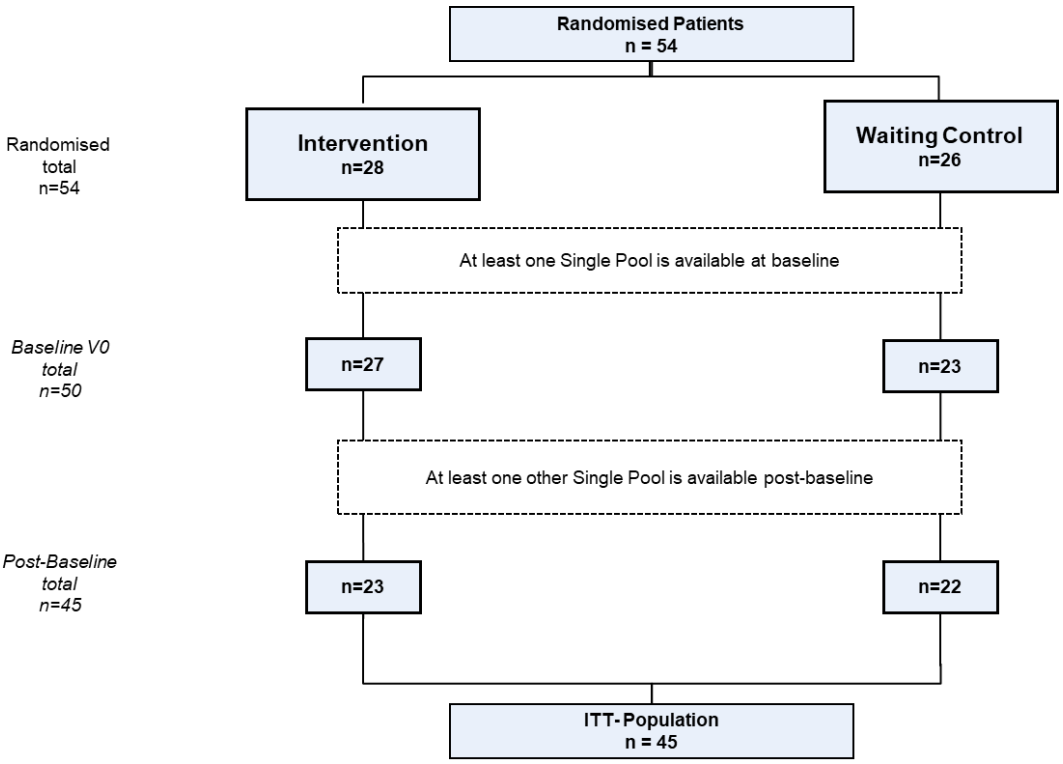
In this chapter we shorty discuss the most important results, for further information we attach the DiaSport Table Listings with all results of the statistical analysis and a power point presentation of all data analyzed. At the time of finalization of the study, we had decided with the statistician, that we would have enough patients enrolled into the study, so that we will have the necessary 26 patients per group included into the study (26 patients in waiting control group, 28 patients in intervention group, 3 patients with drop out).

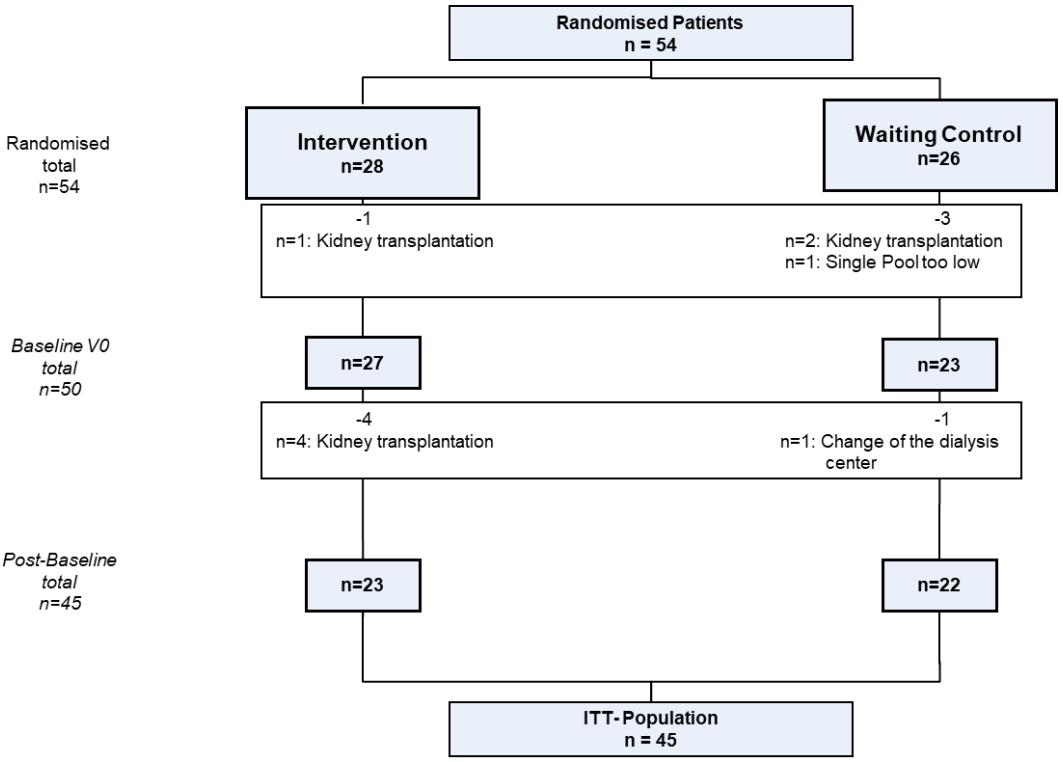
5.1. Patient Populations

5.1.1. Patient-Flow - Intention-to-Treat (ITT) Population

From the 54 patients randomized, the evaluable Intention-to-treat-population consisted of 45 patients, 23 in the Intervention group, 22 in the Waiting-Control group, respectively. Criteria were at least one single pool Kt/V prior and post baseline.

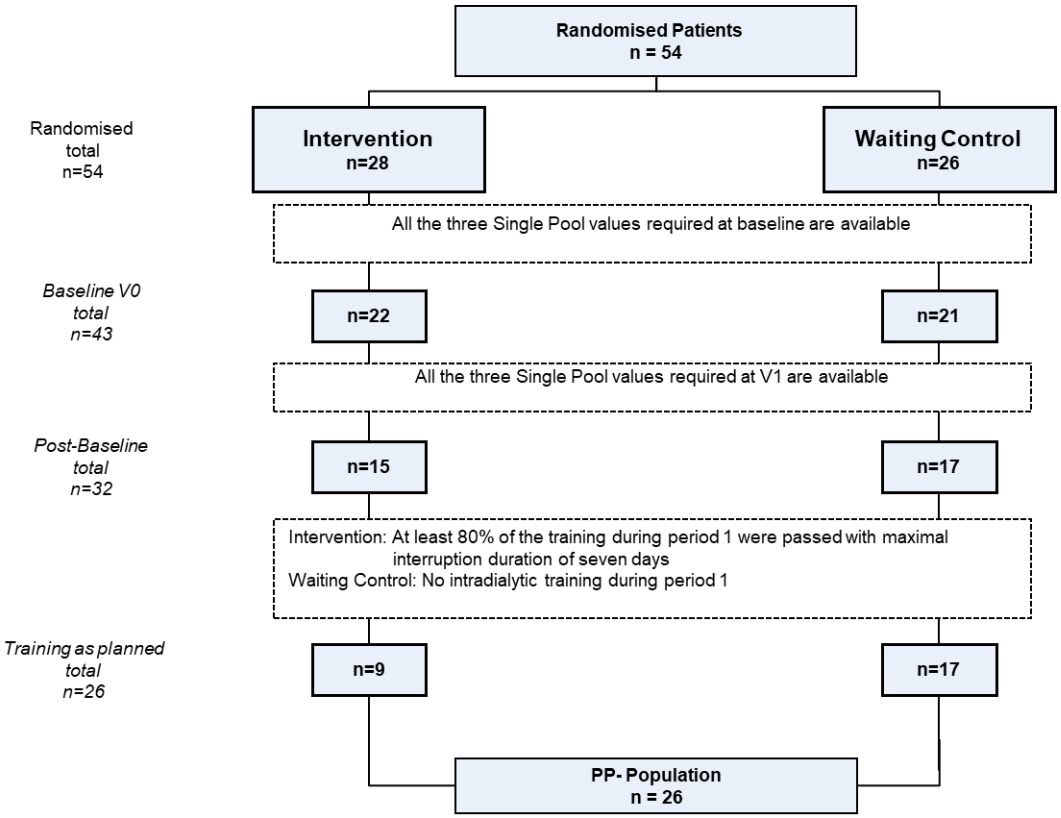
The loss of patients in the ITT population was due to 5 or 2 kidney transplantations, respectively, one patient did not fulfill the inclusion criteria (single pool Kt/V to low) and one changed the center during period 1 and was then lost for study purposes.



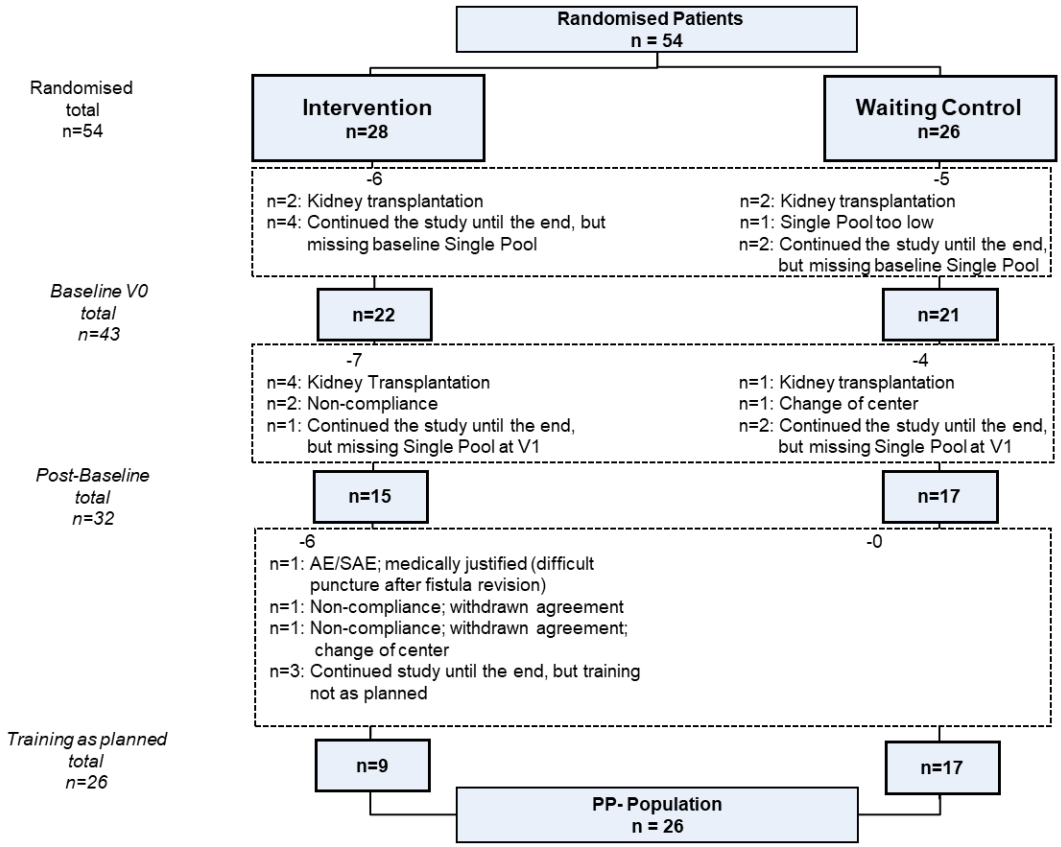

Randomised Patients
n = 54
Randomised
total
n=54
Intervention
n=28
Waiting Control
n=26
-1
n=1: Kidney transplantation
-3
n=2: Kidney transplantation
n=1: Single Pool too low
Baseline V0
total
n=50
n=27
n=23
-4
n=4: Kidney transplantation
-1
n=1: Change of the dialysis center
Post-Baseline
total
n=45
n=23
n=22
ITT-Population
n = 45

5.1.2. Patient-Flow - Per-Protocol (PP) Population

The evaluable Per-Protocol population consisted of only 26 patients, just 9 in the Intervention group and 17 in the Waiting-Control group. Criteria were all three single pool Kt/V prior and to V0 and V1 and at least 80% of the training during period 1 were passed with maximal interruption duration of seven days in the Intervention group.



The loss of patients in the PP in addition to the loss in the ITT population was due to 5 respectively 2 kidney transplantations in the ITT vs the PP Population, in total 3 patients were lost due to missing spKt/V, 4 due to non- compliance, 1 finished the study but did no train as planned, 2 had a change of the dialysis center and one discontinued after fistula revision.


Randomised Patients
n = 54
Randomised
total
n=54
Intervention
n=28
Waiting Control
n=26
-6
n=2: Kidney transplantation
n=4: Continued the study until the end, but
missing baseline Single Pool
-5
n=2: Kidney transplantation
n=1: Single Pool too low
n=2: Continued the study until the end,
but missing baseline Single Pool
Baseline V0
total
n=43
n=22
n=21
-7
n=4: Kidney Transplantation
n=2: Non-compliance
n=1: Continued the study until the end,
but missing Single Pool at V1
-4
n=1: Kidney transplantation
n=1: Change of center
n=2: Continued the study until the end,
but missing Single Pool at V1
Post-Baseline
total
n=32
n=15
n=17
-6
n=1: AE/SAE; medically justified (difficult
puncture after fistula revision)
n=1: Non-compliance; withdrawn agreement
n=1: Non-compliance; withdrawn agreement;
change of center
n=3: Continued study until the end, but training
not as planned
-0
Training as planned
total
n=26
n=9
n=17
PP- Population
n = 26

5.2. Population Strata

The population strata and the population description is shown in the tables below:

Variable by Treatmentgroup	Treatmentgroup						All	
	Intervention (training)			Waiting control				
	N	ColPctN	RowPctN	N	ColPctN	RowPctN	N	PctN
Center								
Essen	3	10.7	50.0	3	11.5	50.0	6	11.1
Freiburg	1	3.57	100	.	.	.	1	1.85
Hamburg	1	3.57	50.0	1	3.85	50.0	2	3.70
Hannover	.	.	.	1	3.85	100	1	1.85
Heidelberg	5	17.9	55.6	4	15.4	44.4	9	16.7
Koeln	6	21.4	50.0	6	23.1	50.0	12	22.2
Leipzig	1	3.57	50.0	1	3.85	50.0	2	3.70
Marburg	2	7.14	66.7	1	3.85	33.3	3	5.56
Memmingen	1	3.57	50.0	1	3.85	50.0	2	3.70
Muenchen	1	3.57	50.0	1	3.85	50.0	2	3.70
Muenster	2	7.14	40.0	3	11.5	60.0	5	9.26
Tuebingen	1	3.57	50.0	1	3.85	50.0	2	3.70
Bonn	4	14.3	57.1	3	11.5	42.9	7	13.0
All	28	100.00	51.9	26	100.00	48.1	54	100.00
Sex of child								
male	23	82.1	60.5	15	57.7	39.5	38	70.4
female	5	17.9	31.3	11	42.3	68.8	16	29.6
All	28	100.00	51.9	26	100.00	48.1	54	100.00
Prior kidney transplantation								
yes	23	82.1	56.1	18	69.2	43.9	41	75.9
No	5	17.9	38.5	8	30.8	61.5	13	24.1
All	28	100.00	51.9	26	100.00	48.1	54	100.00

5.3. Description

	Intervention (training)	Waiting control	Overall	P values[a]
Age				0.3726 (0.5790)
N	28	26	57	
Mean	14.1	14.8	14.4	
Std	3.16	2.83	2.93	
BMI				0.2978 (0.0495)
N	27	23	51	
Mean	19.6	18.7	19.1	
Std	3.74	2.46	3.19	
Single Pool kt/V				0.3726 (0.5790)
N	27	23	51	
Mean	1.7	1.8	1.7	
Std	0.34	0.54	0.44	
PedsQL (Parents) Total Score				0.6892 (0.3762)
	13	11	24	
	72.0	75.0	73.4	
	20.45	15.40	17.99	
PedsQL (Child) Total Score				0.2713 (0.8151)
	22	18	40	
	76.7	81.5	78.8	
	15.22	11.50	13.73	
Reduction of phosphate (%)				0.9545 (0.8151)
	27	23	51	
	41.0	41.6	41.5	
	39.60	37.64	37.97	
Haemoglobin				0.7716 (0.2708)
	25	23	49	
	11.1	11.2	11.1	
	1.68	1.32	1.51	

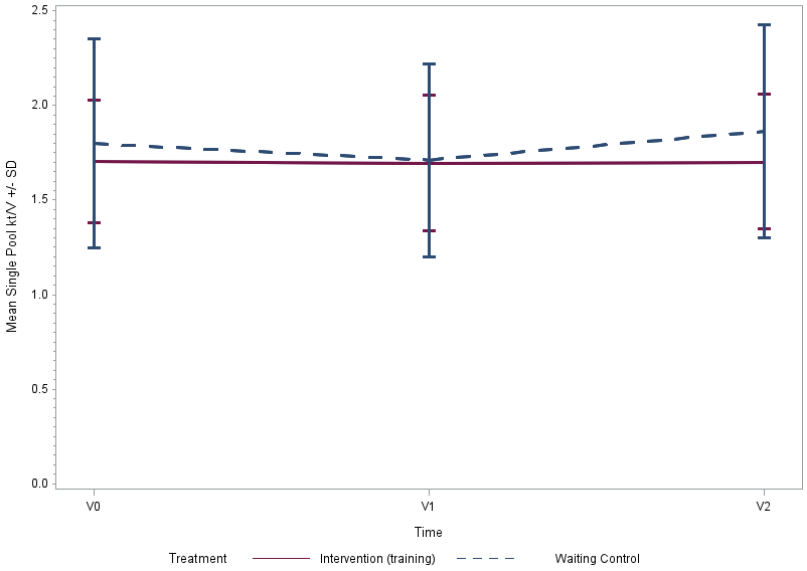
a) T test (F-test of equality of variances). A result for unequal variances is given if the F test is < 0.05).

5.4. Results ITT and PP

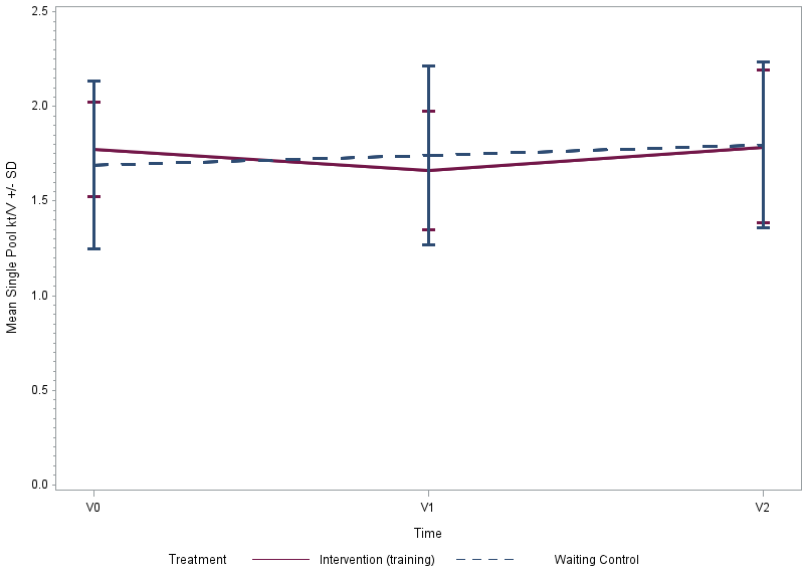
5.4.1. Primary endpoint – Single Pool Kt/V

There was no significant difference in the training group compared to the waiting control group at V0, but also no difference was found at V1 and V2 (see graphs below).

5.4.1.1. Single Pool Kt/V ITT



5.4.1.2. Single Pool Kt/V PP



5.4.2. Secondary endpoints

With regard to all secondary endpoints no significant differences were found. We have attached the statistical report, as well as a power point presentation, so that an extended data review is possible.

5.5. Safety

5.5.1. Adverse Events (AE)

There was no significant difference in number and severity of AEs and SAEs during the training period in both groups and the waiting control period. Especially no bleeding or dislocation of the dialysis needles occurred during the 1670 training sessions.

		Intervention	Waiting Control	Overall
Overall AEs	N	164	154	318
Severity				
mild	N	127	102	229
	ColPctN	77.44	66.23	72.01
moderate	N	32	49	81
	ColPctN	19.51	31.82	25.47
severe	N	5	3	8
	ColPctN	3.05	1.95	2.52
Relation to study intervention				
unrelated	N	122	113	235
	ColPctN	74.39	73.38	73.90
related	N	41	15	56
	ColPctN	25.00	9.74	17.61
unknown	N	1	26	27
	ColPctN	0.61	16.88	8.49

5.5.2. Severe Adverse Events (SAE)

		Intervention	Waiting Control	Overall
Overall AEs	N	164	154	318
Severity				
mild	N	127	102	229
	ColPctN	77.44	66.23	72.01
moderate	N	32	49	81
	ColPctN	19.51	31.82	25.47
severe	N	5	3	8
	ColPctN	3.05	1.95	2.52
Relation to study intervention				
unrelated	N	122	113	235
	ColPctN	74.39	73.38	73.90
related	N	41	15	56
	ColPctN	25.00	9.74	17.61
unknown	N	1	26	27
	ColPctN	0.61	16.88	8.49

6. Discussion

Patients on maintenance hemodialysis (HD) spend significant time, which may total 1000 hours per year, during transport to and at each dialysis session, especially in pediatric and adolescent patients, as there are only few facilities per country and travel times can be long. Hence, they lack spare time to participate in social and/or sport events. Also, chronic HD patients are frequently too exhausted for training after hemodialysis, possess lower endurance and are not necessarily motivated to perform sports and to improve their endurance capacity [1,2]. This results in reductions of functional and cardiopulmonary capacity that encumbers activities of daily life and increases mortality risk [3-6].

Studies focused on activity and exercise in adult maintenance HD patients have demonstrated a positive impact of sports on patient physical performance [1; 7]. Similarly, exercise intervention during dialysis in adults alleviated causes and symptoms of reduced exercise capacity [8,9]. These studies have demonstrated that training during dialysis is regarded as safe, effective, and practical [1,2] and stimulated interest to perform comparable studies in children and adolescents with chronic kidney disease (CKD) [10].

Studies support that children and adolescents benefit from a training intervention leading to an increased aerobic capacity, such as muscle growth [2]. Endurance training during dialysis is indeed possible and safe in the pediatric/adolescent patient, but a specific and individualized training control is extremely necessary [10]. However, it still has to be evaluated on whether an appropriate training for children and adolescents with a high demand character is doable. It became clear, that intra-dialytic training in children and adolescents should address specific individual challenges with respect to training design and motivation. In particular, interventions that occurred before and after dialysis resulted in a high drop-out rate due to motivational reasons and lack of time, especially in adolescents. Also, individualization of training sessions, e.g. time limits, and increase or decrease of workload are necessary points to consider, when performing endurance training during dialysis [2,9,10].

We had expected, that we would be able to proof pilot data that a training program during dialysis would at least be possible to ameliorate the endurance capacity of the patients treated and hence their quality of life. In addition and most importantly, however, we had hypothesized, that training during dialysis would increase dialysis efficacy expressed as single pool Kt/V.

We were able to show, that a training program during dialysis for pediatric patients on maintenance hemodialysis is doable and safe. We experienced no training related (serious) adverse events, which would have hampered the training program. However, we experienced a loss of motivation in most of our patients over the time of the study. This was especially the case in adolescent patients. They obviously did not regard the training as a possibility to increase their quality of life, which we had acknowledged in our previous pilot studies [11]. In the pilot studies, we showed an increase in endurance capacity and thus the patients reported, that they were better be able to participate in normal daily life, but also in social or sport events. In the current study, however, no effect was seen, when watt related workload was measured, or quality of life questionnaires were analyzed (see attached presentation and statistical evaluations).

Also, and most importantly, the primary end point, amelioration of single pool Kt/v, was missed, as were all other secondary endpoints. This was definitively unexpected and of course needs explanation. We have to consider, that the routine care taking of pediatric patients on maintenance dialysis, here especially hemodialysis, was already at a high standard level before the study was started. This is expressed as already high Kt/v levels at V0 for both study groups, and also at V1 for the waiting control group. So maybe, we, the pediatric nephrologists, performed too good before the study, so that an amelioration of values would have been hard to achieve.

However, another reason for the missing measurable effect could be the small number of participants, especially in the Per Protocol group. Only nine patients finished per protocol in the intervention group; expected were at least 26 in this group. But also in the IIT population a low number of evaluable patients were achieved. Even subgroup evaluations (see attached PP Presentation) did not find evidence for group specific advantages. There were several reasons for the missing participants: fewer patients randomized, a significant number of patients transplanted during the trial, some test protocol deviations, the long duration of the study and thus the decrease in motivation of our colleagues to include patients (competing studies with more earnings per patient had started)) and last but not least the low motivation of the patients to train as planned. It was interesting to see a high motivation at the beginning of the training periods, patients in the waiting control group, or patients not

yet included into the study could not wait until training was started. Very soon, however, they felt training to be too much effort, too time consuming and wanted to get back to their routine dialysis procedures. Only a minority of patients asked for further training after the study was stopped (less than 10 %).

The most intriguing experience with this study, however, was the time needed to get the study running (see informations provided above at 4.2.3). We experienced not only a huge gap between patients planned and patients included, which was sometimes due to transplantation or other acceptable medical reasons, but also based on competing studies with more per patient payment. As our study payments were calculated merely 3 years before start of study, payments may have been too small to compete with other studies. However, as the community was very interested in the sport during dialysis study, we definitively could not understand, why some centers were profoundly involved and other centers with a comparable number of dialysis places were not.

Also, monitoring problems have to be mentioned (see point 3.2). We had problems to adequately get data collected and that the monitoring efforts were time consuming. In two centers, we were unable to even install the final eCRF because of data security hazards (in one center Windows XP was still used for the patient data system!). So, the printed CRF versions were used and we, the PI center, had to include the data later into the databank.

We also have to critically ask ourselves, whether the intervention had not enough intensity to force an effect. Endurance-oriented exercise on the stationary ergometer, which is monitored by continuous blood pressure and heart rate measurements as used in many cardiovascular diseases in children and adolescents, has proved its efficacy in this age group of patients with chronic kidney insufficiency [10]. The growing organism has a high adaptation to aerobic performance and is well suited for endurance exercise in an aerobic state [12]. In order to develop a child-appropriate training concept, we had to consider the everyday movements of a child: they perform short, fast movements in an aerobic state, similar to an interval training [13]. Often referred to as playful, this form of exercise is an attractive alternative to classic "high volume training." In addition, it offers numerous combinations in terms of the ratio of “exercise-to-pause” duration, mean intensity and amplitude of intensity to training pauses [14]. In addition to a smaller time investment and rapidly noticeable changes, this form of endurance exercise has demonstrated improvements in performance physiology [15]. So, we had many reasons to use the endurance program as planned for that study and we still think that it is an appropriate method to train during dialysis. We may, however, make the training more interesting, more playful, so that the patients are more interested to stay on track. We had discussed a bike training which would have been accompanied by a computer program (e.g. 30 minute ride through a hilly region). However, we did not use such a program, as we thought it would have been difficult to find appropriate interventions for a pediatric patient population. Nevertheless, as it was harder than expected to motivate patients and medical staff to participate regularly, it might have been better to use e.g. common motivational methods from fitness centers. Here, group training would have been an idea, which was, however, not feasible because of patient randomization timelines and facility circumstances (rooms to small).

Nevertheless, we have to consider, that the trial had not enough power to proof neither an effect on dialysis efficacy nor any of the secondary endpoints. We can only state that it was safe to perform intradialytic bicycle ergometer training and that it did not have a negative effect on the participants. We still think that such an endurance training program would be a positive measure in patients with maintenance hemodialysis, but that it would be necessary to profoundly upgrade the circumstances. It possibly would have been better to perform a study without control group and with a three months training program only. Also, for a future study, motivational aspects need to be considered more carefully. It also has to be taken into account, that pediatric and adolescent patients do not want to perform sports during dialysis, but would much more appreciate adapted sport programs with their friends during their spare time.

We still did not finish the analysis and interpretation of the full training control data (data stored at each training session, like heart rate, blood pressure etc.). All the values will be analyzed in detail with the sports scientists. Here, we may be able to see motivation related changes, e.g. increase in endurance values during the first weeks of study and a decline again thereafter. Also, we maybe able to show positive training related effects, e.g. on long term follow up blood pressure values. All the training data was not stored in the main, but in a different only sports related databank. We will report on that, when the huge amount of data was finally analyzed.

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