Post-market Study Protocol

A randomized, blinded, cross-over trial to evaluate the safety, functional mobility and satisfaction of the microprocessor controlled prosthetic knee component C-Leg4 in transfemoral amputees

C-Leg 3 and C-Leg 4 Study in Transfemoral Amputees

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a post-market study

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1 Overview

During the last two decades many MPK appeared on the market. Despite that additional functionality and safety of MPK over mechanical knee joints are assumed, not for every MPK additional benefit was proven.

The newly developed C-Leg4 aims to provide improved standing function while in the same time offering technology of knee´s previous version (C-Leg-3). Since added functional benefit of a knee joint cannot be anticipated just due to the fact that the knee is controlled by the microprocessor, the aim of this post-market study is to evaluate the safety, functional mobility and satisfaction of the microprocessor controlled prosthetic knee components C-Leg3 and C-Leg4 in comparison with mechanical knee joints. Additional goal of this post marketing study is to improve the methodological quality of research conducted in the field.

2 List of Abbreviations

Abbreviation	Definition
6MGT	6 Minute Gait Test
10mGT	10 Meter Gait Test
ABC	Activities-specific Balance Confidence
ABIS	Amputee Body Image Scale
AE	Adverse Event
AR	Adverse Reaction
CRF	Case Report Form
eCRF	electronic Case Report Form
FSST	Four Step Square Test
HAI	Hill Assessment Index
ITT	Intention-To-treat (ITT)
MPKs	Microprocessor Controlled Knees
MFCL	Medicare Functional Classification Level
NMPKs	Non-Microprocessor Controlled Knees
PLUS-M	Prosthetic Limb Users Survey of Mobility
SAE	Serious Adverse Event
SAI	Stairs Assessment Index
SAR	Serious adverse reaction
PP	Per-Protocol
UAR	Unexpected adverse reaction

3 Background

For the individual with lower limb amputation, it is crucial to select an appropriate prosthetic device which can restore much of the ambulatory function that has been lost and has an impact on patient´s safety as it relates to stumbles, falls and balance.

Several studies investigated changes in ambulation when lower limb amputees walked on C-Leg and non-microprocessor controlled knees (NMPKs). The improvements of self-selected walking speed ranged from 7.3% up to 15% (average difference 0.1m/s) (Orendurff et al 2006, Segal et al 2006, Kahle et al 2008), while the fastest possible walking speed was improved up to 17% (average difference 0.2m/s) (Kahle et al 2008) with C-Leg compared to NMPKs. Although the design of used outcome measures varied throughout the trials as well as the target population, each study reported an increase in walking speed when ambulating with a C-Leg compared to NMPKs. These could be possible explanations why the reported self-selected walking speed of transfemoral amputees fitted with C-Leg ranged from 0.98m/s up to 1.39 m/s (Kahle et al. 2008, Orendurff et al 2006, Segal et al 2006, Bellman et al 2010), while reported values for fastest walking speed ranged from 1.19m/s up to 1.66 m/s (Orendurff et al 2006, Bellman et al 2010). Despite this variety, walking speed is valuable outcome. Walking speed has been shown to be associated with survival among older adults and has been shown to reflect health and functional status (Abellan et al., 2009). Gait speed has been recommended as a potentially useful clinical indicator of well-being among the older adults (Hall et al., 2006). Improvement of 0.1m/s in comfortable gait speed over a 1-year period strongly predicts survival through the subsequent 8 years, with a 58% reduction in relative risk and a 17.7% reduction in absolute risk of death (Hardy et al., 2007). Additionally, an improvement of 0.1m/s in gait speed predicts higher ambulatory category (Perry et al., 1995) and cost reduction (Purser et al., 2005).

Safety and confidence in the prosthesis play an important role in the amputee´s life. Fall always represents a potential harm for health and trust in prosthesis. The fear of falling is one of the major factors for decreased activity, mobility, and quality of life. Miller et al. 2001 reported that among community-living persons with lower extremity amputation, 52% had fallen in the past 12 months, 49% had a fear of falling, and 65% had low balance confidence scores. When using C-Leg compared to NMPKs, stumbling was reduced by 25%, semi-controlled falls by 17% and falling by 10% (Hafner et al 2007). Even a larger decrease with C-Leg compared to NMPKs, namely stumbles by 59% and falls by 64%, was reported by Kahle et al (2008). Limited community ambulators profit from a transition from a NMPK to C-Leg with a decrease in falls by even 80%. K3 subjects reduced the frequency of stumbles by 31% when using C-Leg (Hafner et al 2009). Furthermore, the most recent study reported that falls were reduced by 33% with C-Leg compared to NMPKs (Highsmith et al 2014). Similar observations are further confirmed in other studies (Drerup et al 2008, Wong et al 2012). Finally a case report showed that Berg Balance Scale score and Activities-specific Balance Confidence (ABC) Scale improved immediately with C-Leg after only one hour of training compared to a NPCK (Wong et al 2012).

Performance in descending stairs and ramps is improved with C-Leg compared to NMPK (Hafner et al 2007, Kahle et al 2008, Hafner & Smith 2009). Furthermore, subjects improved their performance in activities of daily living (Theeven et al 2011) as well as overall quality of life (Hafner et al 2007, Kahle et al 2008, Hafner & Smith 2009) with C-Leg compared to NMPKs. This indicated that the use of MPK allows for amputees to participate in a wider range of activities of daily living

and thereby providing a higher participation in their community and hence society. Therefore it is not surprising that a high majority of subjects prefer MPK compared to NMPK.

Evidence collected during the last two decades suggests that in comparison to mechanical knee joints C-Leg improves the user's safety, ability to walk faster, to negotiate stairs, hills and participate in a wider range of activities of daily living. In the same period of time many MPK appeared on the market. Despite this additional functionality and safety of MPK over mechanical knee joints are assumed, not for every MPK additional benefit was proven (Prinsen et al., 2014, Hafner 2015). The newly developed C-Leg4 aims to provide improved standing function while in the same time offering technology of the knee´s previous version (C-Leg-3). Since added functional benefit of a knee joint cannot be anticipated just due to the fact that the knee is controlled by the microprocessor, the aim of this post-market study is to confirm that the microprocessor controlled prosthetic knee components (C-Leg3 and C-Leg4) in comparison to mechanical knee joints can bring additional benefit to the user primarily on level walking and secondary on safety, stairs and hills mobility, activities of daily living, satisfaction and preference. Second study hypothesis is that C-Leg4 can improve primarily users ability to walk on even terrain, and secondly on stairs, hills, as well as to increase safety, satisfaction and participation in activities in daily living.

It needs to be stated that additional goal of this study is to improve methodological quality of the research conducted with prosthetic knee joints. Recent published data are generally rated as providing moderate to low levels of evidence because of structural weakness of the study designs. These weaknesses are mostly caused by low statistical power due to the small sample number and high dropout rates, a lack of blinding, and precise measures with no estimate of minimal detectable changes(MCD) (Orendurff et al., 2013). At least two areas of methodological improvement will be addressed in presented research: 1) blinding of the users, assessors and statistician, and 2) larger numbers of participants will be enrolled.

4 Device information

Both C-Leg3 and C-Leg4 are driven by a microprocessor-controlled hydraulic unit that dynamically adapts the system to all gait speeds in real time. It has a microprocessor controlled swing- and stance control. Customizable software settings and internal sensors enable an intelligent control of the microprocessor-controlled knees – the system always recognizes the specific phase of gait performed by the user. The microprocessor ensures that the damping of the hydraulic unit is always adjusted to the specific situation, from highest safety during the heel strike to the easy changeover to swing. This is always done in real time – irrespective of whether the knee user is walking fast or slowly, or with long or short steps. As a result, the user may move freely and easily whatever the surface – be it on level or uneven ground or stairs or walking on inclines.

With C-Leg3, the swing phase is triggered when following requirements are fulfilled: the knee angle sensor measures that the knee prosthesis is in a fully extended position and there is no flexion movement released. Two strain gauge strips measure the load on the foot. A defined load threshold has to be exceeded that swing phase is released.
C-Leg4 requires following conditions to release to swing phase: Equivalent to C-Leg3 a knee angle sensor measures that the knee is in full extension, and additionally, a disc spring measures very precisely hyperextension of the knee which is a criterion for swing phase release. The knee angle sensor and the disc spring function together as a knee moment sensor, which enables release of

the swing phase independent form a toe load. Together in combination with the position sensor which assures correct positioning of the prosthesis, the movement of the foot can be calculated. This leads to the easier transition from stance to the swing phase. Furthermore, standing with the flexed knee is now easier with C-Leg4.

5 Study objectives

As stated above, for the lower limb prosthesis it is crucial to restore much of the ambulatory function that has been lost. Therefore **the primary objective** is to evaluate the effect of the microprocessor controlled knees (C-Leg3 and C-Leg4) **on the level walking** in comparison to conventional mechanical knees.

The secondary objectives are to evaluate the effect of the microprocessor controlled knees (C-Leg3 and C-Leg4) on safety, self-reported balance confidence, number of stumbles and falls, stairs and hills mobility, activities of daily living, satisfaction and preference in comparison with a non-microprocessor controlled knee.

6 Study design

6.1 Experimental plan

A randomized crossover design will be used in this post marketing study. Amputees currently wearing mechanical prosthesis and fulfilling inclusion/exclusion criteria will be enrolled in the study. After recruiting, functional level, demographic, anthropometric, clinical and "0" baseline data will be collected. The certified prosthetist will evaluate the participants' socket and the foot. If the socket are inadequate (e.g participant has subjective problems, the fitting of the socket is unsatisfactory or insufficient for a MPK fitting), the prosthetist will create and fit a new socket, for others copy of the socket will be created. All participants will be fitted with Otto Bock carbon spring feet, where Triton foot will be the first choice to the highest possible extent. Participants will also receive a foam cosmetics which will be used during the entire study. Four weeks of acclimation period to a new socket and foot will be given. The physical therapy will be provided to ensure the best output of mechanical knee joints. The physical therapy with NMPK will have two mandatory sessions plus one optional one if the participant demands it. The participant will receive training from the study physical therapist on the functions of the NMPK knee for walking on level ground, inclines, declines, up & down the stairs, and uneven ground. Performance will be assessed before (1st Baseline measurement) and 2 weeks after physically therapy sessions (2nd Baseline measurement) to check if the administered therapy had any influence on the outcome. The second data recording will be used as the official baseline measurement ("A phase - measurement with mechanical knee joint").

Afterwards the participants will be randomly assigned to be fitted either with C-Leg4 or C-Leg3. The randomization procedure will be concealed and assigned off-site. The fitting of Otto Bock C-Leg4 or C-Leg3 will be performed by a certified prosthetist and physical therapy will be provided. The physical therapy will include 5 rehabilitation sessions plus one optional to ensure that participants are properly using the microprocessor controlled knee. After the therapy participants will be offered an acclimation period that will last up to 90 days prior to undergoing testing with the MPK ("B phase - measurement with C-Leg4/C-Leg3"). Hafner et al., 2007 suggested the criteria

that MPK user needs to fulfil to be fully acclimatized to MPK. The users are allowed to accommodate until they (1) show stable alignment in the test prosthesis (checked and evaluated by certified prosthetist), (2) require no additional changes to the C-Leg software settings (checked and evaluated by certified prosthetist), and (3) verbally acknowledge and physically demonstrate that they are able to perform "proficient-use" tasks (independently ambulate on level ground, declines, inclines, stairs, and uneven terrain) that each subject previously showed in the mechanical control prosthesis. Once all three criteria are fulfilled, they are asked to wear the microprocessor control prosthesis regularly for a period of 1 month. The number of falls will be measured and documented by the user during the last month the device is used.

After the first follow-up data collection, the participants will cross over to the second MPK. The participants who were fitted with C-Leg4 will cross over to C-Leg3 and vice versa. The physical therapy (2 mandatory + one optional session) will be offered to facilitate the transition to another knee joint. The same criteria will be used to estimate acclimatization with the second MPK joint, which will be used for the period of 30 days, followed by the data collection ("C phase – measurement with C-Leg3/C-Leg4"). During the last phase of the trial, the participants will be returned to their original knee. The physical therapy (2 mandatory + one optional session) will be offered to ensure that the patient can use properly the mechanical prosthesis. One month follow-up period, including the measurement of the number of falls, starts once the acclimation criteria are fellfield. Their preference as well as self-reported tests will be assessed ("2nd A phase – measurement with mechanical knee joint"). Finally, participants will be fitted with their original feet after the last measurements are conducted.

The recruitment of the participant will last up to 6 months. Each participant will be enrolled up to 8 months in the study, depending if the socket and foot are appropriate. The entire flow is described in the figure 1, while the physical therapy and fitting concept in the figure 2.

During each baseline and follow-up visit, approximately 1.5 hours will be needed to complete the testing. Four hours will be needed for fitting new socket, foot and foam cosmesis, two hours for fitting of MPK and 1 hour for re-fitting a mechanical knee joint.

Planed duration of the study is from 01.02.2016 until 31.12.2017.

Blinding of the participants, assessors and statistician

This will be the first clinical study concerning exo-prosthetic knee joints with both, the participant and the assessor, blinded. The blinding of participants is possible since appearance characteristics and performance features of C-Leg3 and C-Leg4 are similar. The prostheses will have same color, shape and no labeling. In addition each participant will be fitted with the foam cosmesis.

The research center will delegate the role of assessor to one trained employee. The assessor will be responsible for evaluating functionality of participants in the performance based tests in all phases of the study. During all performance tests, subjects will be instructed to wear long, wide trousers which will disable the assessor to see the prosthesis and to refrain from giving any comments.

The certified prosthetist and physical therapist cannot be blinded. To fit the knee, adjustments must be made during walking and knee specific rehabilitation sessions; these procedures cannot be carried out in a blinded manner.

The randomization procedure will be concealed from all people involved in the study. The order of the prosthetic fitting and the device fitted will be concealed from the statistician, which will enable blinding of the data analyses. Unmasking will be conducted after completion of the data analysis.

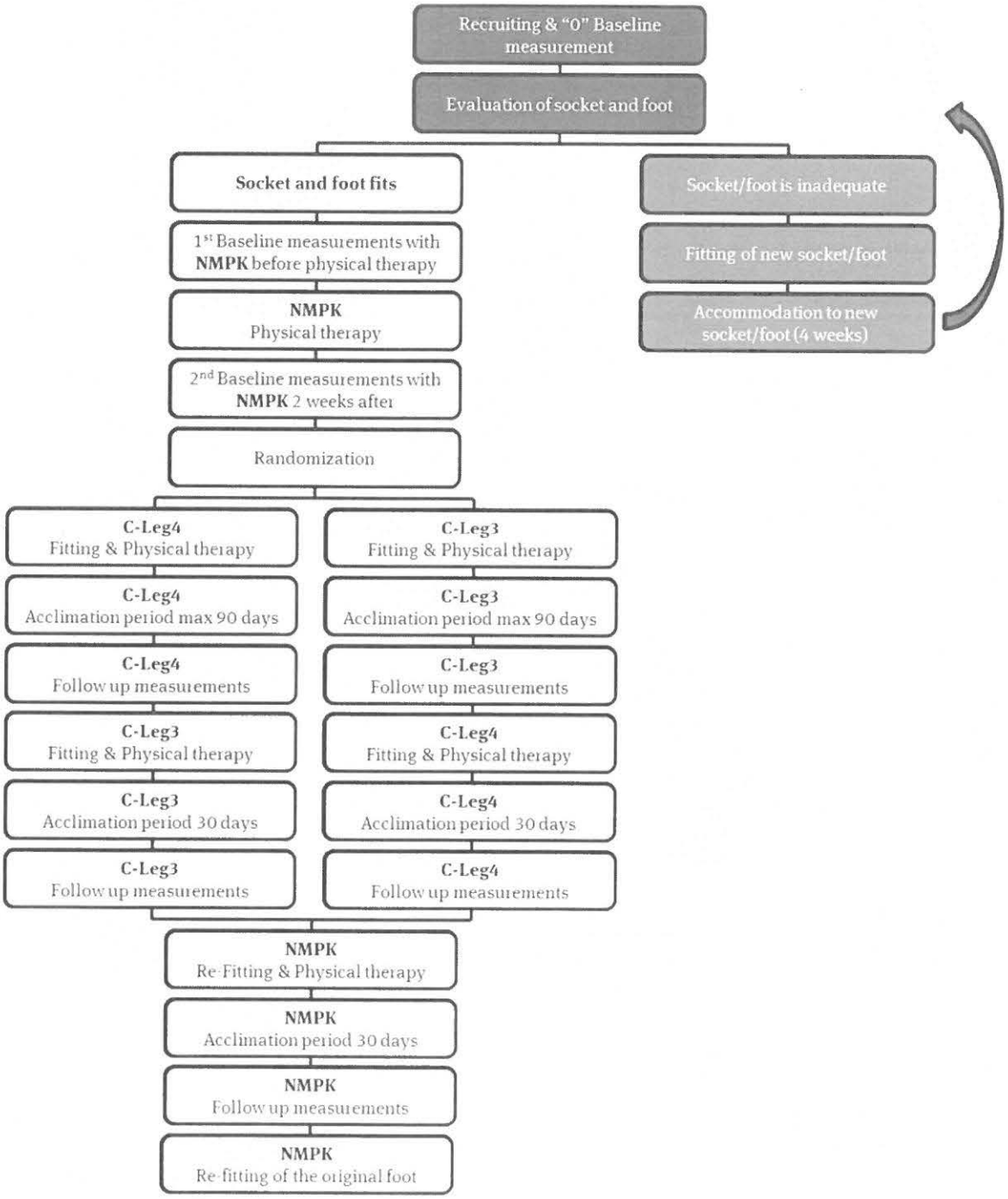

Fig.1 – Patient flow during the entire study

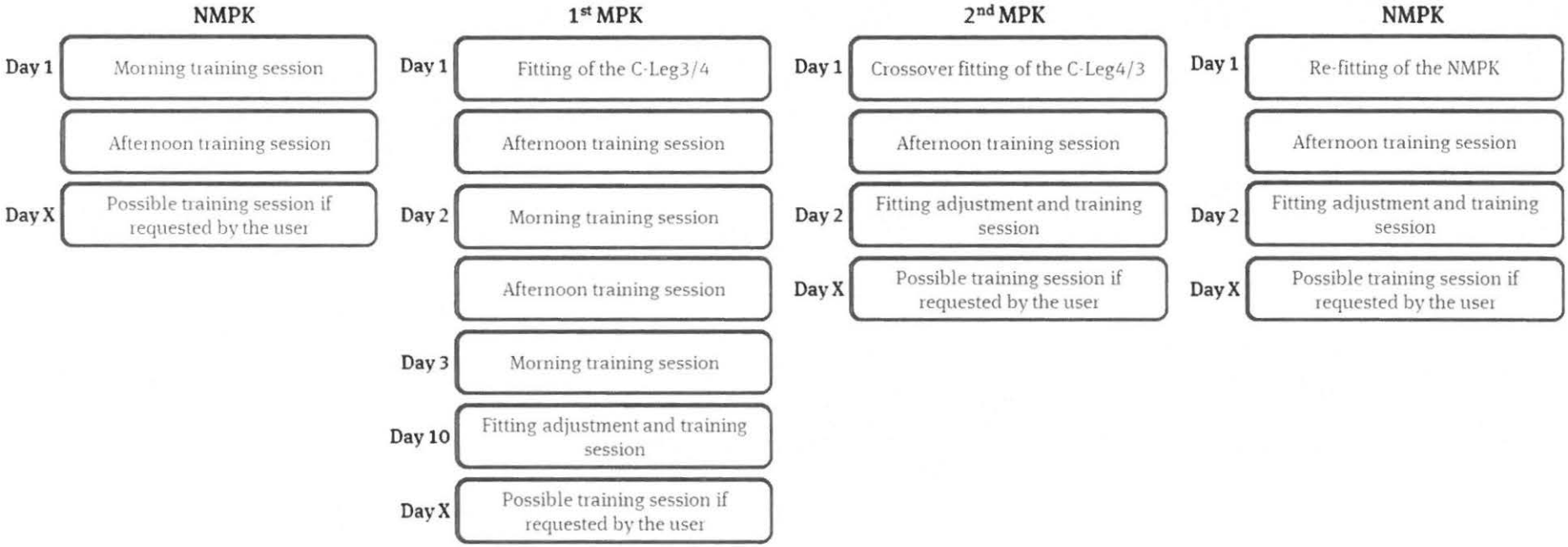

Fig.2: Physical therapy and fitting concept

6.2 Outcome measures

The data on the following outcome measures will be collected at the four assessments:

	A phase - mechanical knee joint	B phase - C-Leg4 or C-Leg3	C phase - C-Leg3 or C-Leg4	2nd A phase - mechanical knee joint
Performance based tests				
6 minute gait test	√	√	√	√
10 meter gait test	√	√	√	√
Stairs Assessment Index (SAI)	√	√	√	√
Hill Assessment Index (HAI)	√	√	√	√
Four Step Square Test (FSST)	√	√	√	√
Self-reported tests				
Activities-specific Balance Confidence (ABC) Scale*	√	√	√	√
Prosthetic Limb Users Survey of Mobility (PLUS-M)	√	√	√	√
Amputee Body Image Scale (ABIS)	√	√	√	√
Number of stumbles and falls	√	√	√	√
Preference of the knee		√	√	√

* instrument validated in German

Primary outcome - Level walking

Walking endurance (assessed with 6min gait test) and walking speed (assessed with 10m gait test) are two important aspects of walking capacity, which is in many groups of patients impaired.

6 minute gait test (6MGT)

The 6 MWT is assessment of the walking endurance and it is associated with aerobic capacity due to the cardiorespiratory strain of completing this test. In this test the participant should walk without physical assistance and cover as much ground as possible during 6 minutes.

Despite the fact that level walking was extensively tested within the studies where participants transitioned from mechanical to microprocessor controlled knee joint, the 6 MWT has never been assessed in this setting.

As shown by Resnik et al., (2011) test-retest reliability (ICC) for unilateral lower-limb amputees is 0.97, while Minimal Detectable Change (MDC) is 45.0 m. Calculation is based on results of 44 participants (mean=332 ± 115m; range 112m to 538m).

Harada et al, (1999) proved test validity in elderly population (mean age=75 years) with gait speed (r = -0.73) and excellent test-retest reliability (r = 0.95). In same population Perera et al., (2006) determined the MDC of 58.31m. Normative data for elderly population (60-69 years old) is 572 m on average for males and 538 m for females (Steffen et al, 2002).

Eright et al., (1998) established reference equations for prediction of the total distance walked during six minutes for healthy adults (based on the results from 117 healthy men and 173

healthy women, aged 40 to 80 years). The median distance walked was 576 m for men and 494 m for women. The 6MGT was significantly less for men and women who were older and heavier, and for shorter men. The resulting gender-specific regression equations explained about 40% of the variance in the distance walked for healthy adults. The suggested equations are:

6MWD (for healthy men) = (7.57 x height$_{cm}$) - (5.02 x age) - (1.76 x weight$_{cm}$) -309m

6MWD (for healthy women) = (2.11x height$_{cm}$) - (2.29 x age) - (5.78 x weight$_{cm}$) + 667m

10 meter gait test (10mGT)

The participant is instructed to walk 10 meters, while the time is measured for the intermediate 6 meters. The participant first walks at a fastest self-selected walking speed. A trial at a maximum safe speed is conducted afterwards. For each speed three trials are collected and the average of all three trials is calculated.

While the 6MGT is associated with aerobic capacity because of the cardiorespiratory strain of completing this test, the 10mGT requires a brief and maximal effort and would, therefore, be expected to be associated with muscle strength (Dalgas 2012).

This test is chosen for several reasons. First, as previously established, a distance-based test is preferred to a time-based test because distance-based tests provide the benefit of a target goal. Second, during this test, gait initiation and termination occur very close one after the other, placing primary emphasis on these more complex aspects of gait. Numerous studies have demonstrated that in the presence of neuromusculoskeletal pathology, changes in motor planning, step length, push-off force, and other parameters adversely affect the initiation and termination of gait (Kahle et al., 2008). Finally, 6 m is the approximate distance of two lanes of traffic.

Kahle et al., reported the results for 10mGT for fastest walking speed for 19 transfemoral amputees for C-Leg (1.27 ± 0.42 m/s) and mechanical knee joints(1.05 ± 0.36 m/s).

Bohannon et al., (1997), reported excellent test-retest reliability for comfortable and fastest gait speeds (ICC = 0.93 - 0.91) in healthy adults (n=230, age 20-79). Normative data for this population are presented in the table below:

	Male		Female	
Age	Comfortable	Fast	Comfortable	Fast
20's	1.39	2.53	1.41	2.47
30's	1.46	2.45	1.42	2.34
40's	1.46	2.46	1.39	2.12
50's	1.39	2.07	1.40	2.01
60's	1.36	1.93	1.30	1.77
70's	1.33	2.08	1.27	1.74

*Comfortable/ fast gait speed in meters/ second for male and females by decade

Perera et al, (2006) published MDC=0.13m/s for elderly population.

Secondary outcome

For safety:

Four Step Square Test (FSST);

The aim of the FSST is to complete a stepping sequence through the 4 squares as quickly as possible. The fastest times on the FSST are done when the participant is able to face the same direction for the entire sequence, which involves stepping forward, backward, and sideways to the left and right. The FSST score of 24s or more is associated with an increased risk of having multiple falls (Dite et al., 2007).

According to Diet et al (2007) normative data for the transtibial amputees who have higher incidence of falling is 32.6s, while non-fallers mean FSST is 17.6s.

Test has excellent test-retest reliability (r = 0.98) in elderly population and concurrent validity with the Timed Up and Go test (r = 0.88) (Dite et at., 2002).

Activities-specific Balance Confidence (ABC) Scale

The ABC Scale is a self-report measurement to assess balance confidence in performing 16 ambulatory activities. Each item is rated on a rating scale that ranges from 0% to 100% where 0% means absolutely no confidence and 100% represents complete confidence. The average score for all 16 items is calculated.

Powell & Myers et al., (1995) showed excellent test-retest reliability (r = 0.92) in elderly population. Normative data for the community dwelling older adults (n = 168, mean age = 70.96) is 79.89 (Huang & Wang, 2009). Validity of the test is established in the same population through excellent correlation between ABC score and Berg Balance Scale (BBS) (r = 0.752) and between ABC score and Timed Up & Go Test (TUG) (r = 0.698).

Self-reported Number of stumbles and falls

With regard to the study objective, the number of stumbles and falls will be evaluated during the last month (30days) that each of the studied devices is used. In practice, a log book will be given to the patient to note all falls and stumbles as well as the circumstances around these events, which will make it easier for the investigator to analyze them. During the baseline measurements the users will be asked to recall number of stumbles and falls, since the log book will be provided to the participant when they enter the study. The investigator will note the number of stumbles and falls that occurred during the last month of use for each of the studied devices in every case report form.

For stair and hills mobility: Stair (SAI) and Hill (HAI) Assessment Index

Stair ascent and descent ability will be measured by using the Stair Assessment Index (SAI). Participants are asked to ascend and descend a 12-step Americans with Disability Act compliant stairwell as they are scored for functional independence and technique by using the 14-level SAI scale. Similarly, users' ability to ambulate a decline will be measured with a custom Hill Assessment Index (HAI). Participants are asked to ambulate on a 5m, 5° downgrade hill at self-selected speed. Participants are scored for independence, technique and step length by using the 12-level HAI scale. Time needed to descent stairs and ramp will be recorded.

The HAI had very good interrater reliability in transfemoral amputee population (intraclass correlation coefficient = 0.97 for NMPKs and intraclass correlation coefficient = 0.99 for C-Leg). HAI score ranged from 3 to 11 (mean=7.6) for NMPK, and from 5 to 11 (mean=8.9) for C-Leg (Highsmith et al., 2013).

The SAI was reported for transfemoral amputees walking on NMPK (for K2 mean=3.3, for K3 mean=4.4) and for C-Leg4 (for K2 mean=9, for K3mean=10.1) (Hafner et al., 2007).

For activities of daily living: Prosthetic Limb Users Survey of Mobility (PLUS-M)

The PLUS-M questionnaire measures prosthesis users' mobility (i.e., their ability to move intentionally and independently from one place to another). The 12 questions assess respondents' perceived ability to carry out specific activities that require use of both lower limbs and cover movements that range from basic ambulation (e.g., walking a short distance indoors) to complex activities (e.g., hiking for long distances over uneven ground).

Normative data for PLUS-M for transfemoral amputees with dysvascular ethology is 42.9 (n=120), with trauma 50.5 (n=266), for mobility grade K2 45.2, for K3 50.5, and for K4 53.8 (n=199). PLUS M showed high test reliability (0.96) (Hafner et al., 2015). PLUS-M demonstrated a strong positive relationship with the PEQ-MS (r = 0.76) and ABC (r = 0.81) (Gaunaurd et al., 2015)

For satisfaction and preference:

Amputee Body Image Scale (ABIS)

The ABIS assesses how an amputee perceives and feels about his or her body experience. The scale addresses several different domains, including: 1) body appearance; 2) body function; 3effective distress; and 4) behavioral avoidance in social situations. The scale produces scores that range from 1 to 100, with low scores indicating the relative absence of a body image concern and higher scores indicating the presence of a more serious body-image concern.

ABIS is proven to be reliable by evaluating the internal consistency of a test instrument (alpha coefficient of 0.80). Reported ABIS data for the transfemoral group (n = 30) had a median of 35.5. (Breakey et al., 1997).

Knee Preference

The user´s knee preference is assessed with the question: "Which prosthesis do you prefer?"

7 Patient population

Unilateral subjects having transfemoral amputation or knee-disarticulation will be enrolled in the study.

Inclusion criteria:

- Person is >18 years old.
- Person is a unilateral transfemoral or knee-disarticulation amputee with stabilized residual limb.

- Person is a K2, K3 or K4 ambulator based on Medicare Functional Classification Level (MFCL) (see appendix).
- Person is currently fitted with a prosthesis using a non-microprocessor controlled prosthetic knee for at least 6months.
- Person was never fitted with microprocessor controlled prosthetic knee joint.
- Person is willing and able to independently provide informed consent.
- Person is willing to comply with study procedures.
- Person wears prosthesis daily and ≥ 8 hours/day.
- Person is walking on average 1km/day.
- Person is walking not slower than 3km/h (~0.8m/s) (based on 10m walk test conducted during recruiting).
- Person is walking on level ground alternating steps (step over step manner).

Exclusion criteria:

- Person is under 18 years of age.
- Person who weigh more than 136kg.
- Person who weigh less than 50kg.
- Person who is pregnant.
- Person has a history of chronic skin breakdown on the residual limb.
- Person has conditions that would prevent participation and pose increased risk (e.g. unstable cardiovascular conditions that preclude physical activity such as walking).
- Person falls ≥ once a week due to the reasons that could not be corrected by the new prosthesis (for ex. problems with vestibular system).
- Person is using under arm axillary crutches or walker.
- Person in an emergency, life threatening situation.
- Person is unwilling/unable to follow instructions.
- Person who is not available to follow the entire study protocol.
- Person who is participating in another study or intends to participate in another study during this study´s duration.
- Person who cannot personally provide their consent.
- Person who is not wearing prosthesis 8hours/day on average.
- Person who has a score on 10m walk test at 3km/h (~0.8m/s) (based on 10m walk test conducted during recruiting).
- Person who walks on average less that 1km per day.
- Person who is not able to walk on level ground alternating steps (step over step manner).

<u>Drop out or early termination of the study</u>

Subjects can withdraw from the study at any time and for any reason. In case of early termination, the investigator must document the reasons as completely as possible. The investigator can temporarily or permanently discontinue the subject's study participation for any reasons that are in the subject's best interest, particularly in cases of serious adverse events. If a subject is lost to follow-up, the investigator will use all available means to get into contact with him or her. After three weekly telephone reminders, the subject will be recorded as lost to follow-up.

The investigator will fill in the reason for the drop out or early termination of follow-up in the case report form.

8 Statistics

8.1 Number of patients & study sites to enroll and rationale

Since the primary outcome measure 6MGT will be used for the first time in this setting, the number of patients who will be enrolled in the study cannot be calculated prior to study beginning. Twenty patents who fulfill inclusion/exclusion criteria, will be initially recruited and will follow the above described study design. Based on the 6MGT results from these twenty participants the total number of patients to be enrolled will be calculated.

Relaying on an approximated normal distribution, the following formula is used for cross-over design studies (Jones, B. and Kenward, M. 2015):

$$n = 2 * (\sigma^2/\Delta^2) * (z(\alpha'/2)+z(\beta))^2 + z(\alpha'/2)^2/2$$

where,
$\alpha = 0.05$
α' = Bonferroni-adjusted α
$1-\beta$ = desired power, $\beta=0.80$
σ = standard deviation (within-patient)
Δ = expected difference

The potential dropout rate of 25% during the study will be taken into account when calculating the necessary patient number to compare prostheses.

8.2 Method used to take into account missing, unusable or invalid data

If data are missing, illegible or incoherent, requests for further information will be sent to the investigator in question. Computerized data validation programs will be developed and implemented to ensure the database's consistency and validity. If errors or inconsistencies are detected, requests for further information will be sent to the investigator in question; any changes will then be integrated into the database by the person in charge.

8.3 Populations for analysis

The analysis will be performed on the intention-to-treat (ITT) population and then on the per-protocol (PP) population. The ITT population is defined as all the patients randomized into their randomization group, regardless of the treatment received or their outcome in the study. The PP population is defined as all the patients in the ITT population without any major protocol deviations.

8.4 Statistical analyses

Patient characteristics: Quantitative variables will be summarized using standard descriptive statistics (average, standard deviation, median, minimum and maximum, first and third quartile). Qualitative variables will be described using group sizes and frequencies. When relevant, 95%confidence intervals will be given. Patient characteristics at enrolment will be presented and

compared in each group to ensure the groups are initially comparable. The features of any patients lost to follow-up will be studied.

Analysis of primary and secondary outcome measures: For the outcomes being evaluated, the below listed assessment is considered as the "final point":

- after 2nd base line measurements with non-microprocessor controlled knee prosthesis
- after up to 90 days of the first MPK prosthetic use when the user is filly accommodated
- after 30 days of the second MPK prosthetic use
- after 30 days of use of the non-microprocessor controlled knee prosthesis

To evaluate the primary objective, the 6MGT and 10mGT results will be compared between the three prostheses.

Because this study uses a cross-over design, the potential carry-over effect will be tested to determine if an interaction exists between the three prostheses using a paired Student's t-test. If the effect is significant, only the first period will be analyzed using a paired Student's t test or the non-parametric Wilcoxon test if the normality and homogeneity of variances assumptions are not met. If the effect is not significant, the period effect and prosthesis effect can then be tested using repeated-measures ANOVA or Friedman's ANOVA if the normality and homogeneity of variances assumptions are not met. If Friedman's ANOVA is significant, a series of Wilcoxon Signed-ranks tests will follow-up with manual Bonferroni correction.

To evaluate the secondary objectives, the prostheses will be compared on the following criteria:

- Four Step Square Test time
- Stair (SAI) and Hill (HAI) Assessment Index score
- Activities-specific Balance Confidence (ABC) Scale score
- Self-reported Number of stumbles and falls
- PLUS-M score
- Amputee Body Image Scale (ABIS) score
- Knee Preference

The same process will be used for the secondary outcome (Four Step Square Test, Stair (SAI) and Hill (HAI) Assessment Index, Activities-specific Balance Confidence (ABC) Scale, Self-reported Number of stumbles and falls, PLUS-M and Amputee Body Image Scale (ABIS)) as for the analysis of the primary outcome measure. Because this study uses a cross-over design, the potential carry-over effect will be tested to determine if an interaction exists between the prostheses. If there is no significant interaction, the period effect and prosthesis effect will then be tested. If there is a significant effect, only the first period will be analyzed. The knee preference will be expressed in percentages.

9 Study sites and patient recruitment

The study will start with two sites, one in Austria - Orthopedic Rehabilitation Center SKA Zicksee and one in Belgium - Physical Medicine and Rehabilitation Clinic UZ Leuven. Each site will recruited up to 10 participants. The recruitment of study participants for the Austrian study site will be carried out by the PI, who will offer the enrolment to the study to patients treated at Rehabilitations Center SKA Zicksee (see inclusion criteria). The recruitment of study participants for the Belgian study site will be done by PI, who will phone and have a consultation with former patients of

Clinics for Physical Medicine and Rehabilitation, UZ Leuven. Enrollment period of initial 20 participants will be 6months, but can be extended if insufficient number of patients is recruited. Depending on the estimated sample number is calculated additional study sites and patients will be enrolled. The responsible ethic committees will be informed about enrolment of additional number of sites/patients via amendment.

10 Randomization

The randomization will be performed in random permutated blocks by allocation order. A randomization sequence will be integrated into the electronic case report form so as to define the randomized treatment order (C-Leg3 or C-Leg4) and provide the investigator with this information during the enrolment visit.

#	Research site	Number of subjects to enroll
1	Rehabilitations center SKA Zicksee Prim. Priv. Doz. Dr. Stephan Domayer, PhD	10
2	Physical Medicine and Rehabilitation Clinic UZ Leuven Dr. Charlotte Kiekens	10

11 Risk benefit analysis

According to external adverse event databases the most prominent risk that comes with the use of MPCK is the risk of falling. This is in agreement with the published literature suggesting that the amputee population presents an increased risk of falling. Therefore these patients demand a high level of safety to be provided by the prosthesis they are supplied with.

In the study of Hafner et al (2007) participants reported that frequency of stumbling was reduced by 25%, frequency of semi-controlled falling by 17% and frequency of uncontrolled falling by 10% with C-Leg compared to NMPKs. Also Hafner et al (2009) observed improvements in safety with C-Leg compared to NMPKs: for K3 population, significant reduction of stumbles and for K2 population significant reduction of uncontrolled falls. These findings are supported by the study of Kahle et al (2008) where the number of self-reported stumbles decreased by 59% and the number of self-reported falls decreased by 64%.

Beside the studies described above, Highsmith et al (2010) analyzed four additional studies on safety in his review article. Three of them reported significantly improved balance with C-Leg compared to NMPKs. The study of Bellmann et al (2010) observed that C-Leg never collapsed compared to NMPKs during all tested condition such as walking, sudden stopping, sidestepping, stepping on object and tripping by disrupting swing extension. In summary, the authors concluded that users should experience a reduction in stumble and fall events together with improved balance as a result of receiving C-Leg (Highsmith et al 2010).

Since their market introduction in 1997, over about 51 500 Otto Bock C-Legs were sold. Regarding 753 critical reclamations recorded internally since 2002 and 19 adverse events recorded externally since 1997 the overall incidence rate is rather small (1.5%). Secondary, the reviewed literature suggests that subjects fitted with a C-Leg not only experience an improvement in per-

formance and satisfaction but also have a reduced risk of falling. Therefore, the risks associated with the use of the device are acceptable when weighed against the benefits to the patient.

12 Management of adverse events

12.1 Definitions

Adverse event (AE): any untoward sign in a person who participates in biomedical research, whether or not it is considered related to the study or to the experimental device being studied.

Serious adverse event (SAE): the event is considered serious if it results in any of the following outcomes:

- Death
- Life-threatening (immediately life threatening at the time of the event and independent of the consequences of a corrective or palliative treatment)
- Disability or permanent impairment
- Hospitalization
- Prolongation of existing hospitalization
- Congenital deformity/anomaly
- Potentially serious event (adverse clinical event or laboratory result that is serious or considered as such by the investigator).

Adverse reaction (AR): any untoward and undesirable reaction related to an experimental device or any incident that could have led to this reaction in a study participant or a device user if appropriate measures had not been taken.

Serious adverse reaction (SAR): serious adverse reaction that is attributable to an experimental device.

Unexpected adverse reaction (UAR): adverse reaction where the nature, severity, intensity or progression is not consistent with the information included in the instructions for use or instruction manual if the device is CE marked and in the protocol or investigator's brochure if the device is not CE marked.

Imputability: relationship between the AE and the device being studied. If an AE is related to the experimental device, it becomes an AR. The following factors will be taken into account when determining imputability:

- Sequence of events
- The AE resolves when the device is removed and/or reappears when it is put on again
- Knowledge of a similar historical event during the use of the device or a device in the same class
- Existence of another etiology.

Severity: The severity of the AE will be evaluated by the investigator based on the following classification:

- Grade 1 - Minor: AE that is generally transient and has no after-effects on normal activities
- Grade 2 - Moderate: AE that is troublesome enough to affect normal activities
- Grade 3 - Serious: AE that considerably modifies the patient's normal activity routine, or that is disabling or life threatening.

Any Note: The severity criteria must not be confused with the seriousness criteria that serve as a guide for defining declaration requirements.

12. 2. Investigator's role

During the entire patient follow-up period, any AE that occurs to a person during the study period must be followed until it resolves or is deemed permanent. The investigator must explore the possibility that an AE has occurred at each follow-up visit.

Any AE, regardless of whether it is related to the study, must be documented. Any change in the severity, relationship with the medical device, procedures required to treat the event or progression must be monitored and documented.

Any SAE, no matter its causal relationship with the studied device must be declared to the sponsor on the form provided for this purpose in the case report form within 24 hours of its occurrence (or as soon as the investigator becomes aware of it). The initial declaration may be followed by relevant additional information within 7 days.

12.3. Sponsor's role

The sponsor evaluates the causal relationship of the AE, any adverse event where the investigator or sponsor believes that a causal relationship with the experimental device may reasonably be expected, is considered as a suspected adverse reaction. If the sponsor and investigator have differing assessments, both opinions will be listed on the declaration sent to the competent authority, if this declaration is needed).

13. Monitoring of clinical trial

The study site is required to conduct the study in accordance with the protocol, all applicable laws and Federal regulations and any conditions or restrictions imposed by the reviewing ethics committee. The Clinical Project Manager will ensure proper monitoring of the study with special attention to verification of all clinical requirements, adherence to protocol, good clinical practices and compliance with applicable government and institutional regulations. The investigator will provide the monitor access to all necessary records to ensure the integrity of the data.

13.1 Study monitors

The investigation will be monitored on a continuing basis through the course of the clinical trial. The Clinical Project Manager will serve as clinical monitor.

13.2. Site visits

Site initiation visits will be made by the Clinical Project Manager to review the study protocol and documentation requirements with the investigator and hospital support staff involved with the study. The project manager will ensure that all researchers involved in the project have adequate training.

Ongoing monitoring visits of the investigational center(s) will be conducted to compare the data recorded in the CRFs with the information contained in the original source documents (source data verification). For the following items, this check will be 100%:

- participant´s identification number
- participant signed informed consent obtained
- participant´s eligibility criteria (inclusion and exclusion criteria)
- efficacy variables
- medical record of Adverse Events

For all other items, at least 20% of the data will be checked.

Additional management of the clinical sites will be achieved by communications via letter, fax, electronic mail and/or telephone.

Site close-out visit will be conducted after all subjects have been enrolled and follow-up has been completed or if deemed necessary.

13.3. Data collection & review

Two forms of CRF will exist: electronical CRFs for Investigators and Assessors and paper CRFs for prosthetists and physical therapists. The reason for this is separation is that treatment will be concealed from assessor but not from prosthetist and physical therapist and secondly to ease the data collection data analysis.

An electronic case report form (eCRF) will be developed by eClinicalOS (Merge, 4000 Aerial Center Parkway, Suite 101 Morrisville, NC 27560).

The CRFs are created in English, but the questionnaires: Activities-specific Balance Confidence (ABC) Scale, PLUS-M score, Amputee Body Image Scale (ABIS) and patient´s logbook are translated in the country's local language.

CRFs must be completed after every visit for each subject enrolled into the study. All forms must be filled out completely. An explanation must be provided for any missing data points. Correction of data in the paper CRFs should be made by crossing out the incorrect data with a single line and writing the correct values next to those crossed out. Incorrect entries must not be obliterated. Each correction must be initialed and dated by the person making the correction. All CRFs must be signed and dated: electronical by the principal investigator, and paper ones by responsible prosthetist or physical therapist.

All CRFs will be reviewed for completeness and clarity. Queries for missing or unclear data will be made as necessary throughout the study. Otto Bock Healthcare Products GmbH may request further documentation such as physician notes when complications or malfunctions are observed and reported.

The Clinical Projects Manager will ensure that the study is properly implemented according to the procedures defined in the protocol and in accordance with Good Clinical Practices, along with applicable regulatory measures.

The Clinical Projects Manager will visit each center in order to:

- Check if the protocol is being followed
- Verify if all AE and SAE have been declared

The investigators commit to allowing audits to be performed by the sponsor and to potential inspections being performed by competent authorities. All data, documents and reports can be the subject of audits and regulatory inspections.

14. Study Discontinuation

14.1. Investigational Site Termination

Otto Bock Healthcare Products GmbH reserves the right to terminate an investigational site for any of the following reasons:

- Failure to secure Informed Consent from a subject enrolled into the study
- Repeated protocol violations
- Repeated failure to complete Case Record Forms on a timely basis
- Failure to report Adverse Events on a timely basis
- The investigator requests discontinuation

If the study is prematurely terminated or suspended for any reason, study participants will be informed promptly and, where required by the applicable regulatory requirement(s), the relevant regulatory authority(ies) will be informed. The ethics committees will be informed promptly and provided with a detailed written explanation for the termination or suspension.

14.2. Premature Discontinuation of the complete study

If the study is prematurely terminated or suspended, the Project Manager, on behalf of Otto Bock Healthcare Products GmbH, will inform promptly the investigator/institution, and, if applicable, the regulatory authority(ies) of the termination of suspension and the reason(s) for the termination or suspension. The ethics committees will be informed promptly and provided with a detailed written explanation for the termination or suspension by the Project Manager, on behalf of Otto Bock Healthcare Products GmbH, or by the investigator/institution, as specified by the applicable regulatory requirement(s). Some of the reasons for premature termination of the study are:

- if the safety of the participants is jeopardized (eh. many falls and stumbles reported), and
- if the users can not show "proficient use" of the intervention devices (e.g. users are not able to ambulate on even and uneven terrain, stairs, hills, and to use their prosthesis in everyday life in the same extend as shown during the recruitment).

15. Ethical considerations

15.1. Research ethics committee

In accordance with current laws of the countries where study will be conducted, the protocol will be submitted to the Research Ethics Committee for an opinion. No patient can be enrolled before the authority has approved the study and the sponsor has held the study launch meeting.

15.2. Patient information and consent

Patients will be informed completely and honestly, using easily understood language, of the objectives and constraints of the study, the potential risks faced, required monitoring and safety

measures, their right to refuse to participate in the study and the possibility of withdrawal at any time.

All of this information is included on the information sheet and consent form given to the patient. The patient's free, informed and written consent will be collected by the investigator before enrolment in the study. A copy of the information and consent form, signed by both parties, will be given to the patient; the investigator will keep the original form. At the end of the study, a copy will be placed in a tamperproof sealed envelope containing all of the consent forms; this envelope will be archived by the sponsor.

15.3. Subject compensation

All subjects participating in this pilot study will receive refund for their travelling costs and time expenditure (15€/ hour during the visits ~ 660€ intotal). The remuneration shall be assigned in an all-inclusive payment upon completion of the study.

Otto Bock Healthcare Products GmbH will provide sockets, carbon spring feet, microprocessor controlled knee joints (C-Leg3 and C-Leg4) and foam cosmesis. The participants will have the opportunity to keep the sockets and cosmesis, while the knees and feet will be returned to the manufacturer.

15.4. The clinical investigator

The Investigator must fulfil all requirements as stated in ISO 14155-1, Good Clinical Practice (GCP) and law of the country where the study is conducted. He/she is responsible for the conduct of the clinical trial and is responsible for the clinical well-being of the subjects involved.

16. Disclosure of data and publication policy

By signing the final protocol, every participating investigator agrees to keep all information and results concerning the study and the investigational product confidential. The confidentiality obligation applies to all personnel involved at the investigational site. Public presentation of study results requires mutual agreement between the investigator(s) and Otto Bock Healthcare Products GmbH.

Otto Bock Healthcare Products GmbH may disclose data derived from the study to other investigators and domestic or foreign regulatory authorities.

All patient related data are recorded in a pseudonymized manner.

The originals of the completed CRFs will be collected by monitor during monitoring visits or sent to the project manager after each assessment with each subject. Copies of completed CRFs and documentation of Informed Consent will be retained by the Investigator together with the subjects' notes.

Copies of all study documents will be retained by the Otto Bock and investigator for 15 years following the end of the study or earlier if approved by Otto Bock.

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18. Appendix

Medicare Functional Classification Level (MFCL) description	
K0	Does not have the ability or potential to ambulate or transfer safely with or without assistance and a prosthesis does not enhance quality of life or mobility.
K1	Has the ability or potential to use a prosthesis for transfers or ambulation on level surfaces at fixed cadence. Typical of the limited and unlimited household ambulator.
K2	Has the ability or potential for ambulation with the ability to traverse low-level environmental barriers such as curbs, stairs, or uneven surfaces. Typical of the limited community ambulator.
K3	Has the ability or potential for ambulation with variable cadence. Typical of the community ambulator who has the ability to traverse most environmental barriers and may have vocational, therapeutic, or exercise activity that demands prosthetic utilization beyond simple locomotion.
K4	Has the ability or potential for prosthetic ambulation that exceeds the basic ambulation skills, exhibiting high impact, stress, or energy levels, typical of the prosthetic demands of the child, active adult, or athlete.