Drug Regulatory Affairs

actibelt®

Briefing Book
for the EMA Qualification of novel methodologies for drug development

Author(s)/reviewer(s): Daumer M, Lederer C, Aigner G, Neuhaus A, Schneider M, Clay I, Natt F, Murphy T, Maier P, McGovern P, Bos J, Roubenoff R

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List of abbreviations

3D	3-dimensional
400m WT	400 meter Walk Test
6MWT	6 Minute Walk Test
AOR	Adjusted odds ratio
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
CE	Conformité Européenne
COPD	Chronic obstructive pulmonary disease
CPU	Central processing unit
DCO	Digitally controlled oscillator
DLR	German National Aeronotics and Space Research Center (Deutsches Zentrum für Luft- und Raumfahrt)
EU	European Union
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
ETH	Eidgenössische Technische Hochschule Zürich (CH)
FDA	Food and Drug Administration (USA)
FPFV	First patient first visit
HTA	Health Technology Assessment

IMI	Innovative Medicines Initiative (https://www.imi.europa.eu/)
IPD	Individual patient data
ITF	Innovation Task Force
KSS	Kraftschlussschalter (open/close status of belt)
LMU	Ludwig-Maximilians-Universität München
MEMS	Micro-electro-mechanical system
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NIH	National Institutes of Health
NRTL	Nationally Recognized Testing Laboratory
OSHA	Occupational Safety and Health Administration
PRO	Patient reported outcome
QoL	Quality of Life
RCT	Randomized controlled trial
RCT2	actibelt version RCT number 2
RFID	Radio-frequency identification
RISC	Reduced instruction set computing
RRMS	Relapsing-remitting multiple sclerosis
SCC	Standards Council of Canada

SGS	Société Générale de Surveillance
SLCMSR	Sylvia Lawry Centre for Multiple Sclerosis Research
SPPB	Short physical performance battery
SVR	Support Vector Machine Regression
TUM	Technische Universität München
USA / US	United States of America
USB	Universal Serial Bus
VA	Veteran Affairs
WHO	World Health Organization
WT	Walk test

1 Introduction

1.1 Summary

Trium Analysis Online GmbH (Trium), Sylvia Lawry Centre for Multiple Sclerosis Research (SLCMSR) and Novartis AG (Novartis) are partnering in a multi-year strategic collaboration to gain regulatory acceptance for accelerometry-based primary endpoints as measured by the actibelt in pivotal clinical trials in mobility restricting diseases.

The actibelt initially was developed and manufactured based on collaboration between Trium and SLCMSR in 2005 (Daumer 2007). When performing analysis on a collection of Multiple Sclerosis (MS) clinical datasets, SLCMSR found and confirmed deficiencies in currently used endpoints (EDSS, Ebers 2008) and surrogates (MRI, Daumer 2009). SLCMSR therefore decided to focus on alternative objective measures of disability (accelerometry based) rather than on the application of bio-statistical methods on conventional scores. As a result, a 3D accelerometer based technology, named actibelt, was developed to allow objective assessment of disability in a real-world setting that is reflective of a patient's day-to-day activities. The current version of the actibelt, RCT2, is manufactured by Trium.

The actibelt RCT2 is a device embedded in a belt buckle and is comprised of an instrumented belt and associated hardware and firmware that collect 3D acceleration data and belt closure status. The belt is intended to be worn by a patient as directed by a health care provider. The data is intended to be transferred to a system where it can be stored and used to retrieve information related to mobility. The technology integrated into the actibelt allows it to be capable of long-term (8 weeks) and continuous monitoring of human motion without need for recharging or other user interaction. A set of validated algorithms has been developed to extract relevant functional parameters including step numbers and gait speed. To date, actibelt has been used for research in various clinical fields (e.g., neurology, musculoskeletal, cardiovascular) as well as aerospace research. In addition, our partner, Novartis has integrated the actibelt RCT2 into two international phase 2 trials in hip fracture recovery and sarcopenia and one local trial in Germany in COPD to generate exploratory endpoints related to mobility (see Appendix D).

Trium approached the EMA Innovation Task Force (ITF) on 22 July 2016 to obtain advice on the process on the potential acceptability of real-world walking behavior measured by actibelt as a primary endpoint in pivotal clinical trials in diseases where limited mobility forms the major burden for patients. Upon submission of the Briefing Package, the ITF noted that the proposed technology is rather advanced and multiple trials are ongoing using this technology,

and therefore recommend that the sponsor pursue a formal Scientific Advice or Qualification Procedure.

In order to have continuous successful development, we are following the recommendation of the ITF from 17 November 2016 to request an EMA qualification procedure with the goal of achieving acceptance of real-world walking speed and behavior measured by actibelt as indicators of the severity, progression, and response to treatment of various diseases that cause loss of mobility and independence. In an initial stage, we would like to obtain advice on the next steps toward having such parameters extracted from mobile accelerometry to be accepted as primary endpoints in pivotal clinical trials for diseases where mobility is a concern.

1.2 Intended Use

Trium would like to qualify the following intended use:

A change in real-world walking speed in diseases where mobility is a concern measured by a mobile accelerometer for seven consecutive days for use as primary endpoint to determine efficacy of a drug of investigation in pivotal clinical trials.

The change in real-world walking speed, that is considered clinically relevant:

- *For Multiple Sclerosis: 0.1 m/s*
- *For recovery after surgical treatment of hip fracture : 0.1 m/s*
- *For Sarcopenia: 0.1 m/s*

The threshold value of 0.1 m/s is proposed as a threshold that Trium believes would translate into a clinical meaningful change in real-world walking speed across the above listed conditions and beyond, where impaired mobility forms the major burden of disease. Trium believes that mobility and gait speed, being a central facet of independence and quality of life, has far wider relevance, and the universality of the proposed threshold should be investigated for specific severities or subpopulations in other mobility impaired indications.

1.3 The need for improved endpoints for mobility-restricting diseases

There is a growing need from both industry and academia to develop new endpoints for mobility that will enable better clinical decision making (Clay Preprint). The need for more reliable endpoints to determine clinical efficacy of a drug in MS clinical trials has been recognized by the EMA (EMA Guideline; Guideline on clinical investigation of medicinal

products for the treatment of Multiple Sclerosis). The approach we would like to discuss is the measurement of continuous mobility instead of clinical short tests (e.g., 6 Minute Walk Test, 6MWT; 400 meter Walk Test, 400m WT). Mobility is already incorporated into the EDSS score for MS and mobility in general is a relevant readout for many indications.

Mobility is a broad term describing our ability to move freely within our environment, however, we believe that the most important aspect of mobility, and the focus of this Briefing Book, is walking. We further divide this into "walking ability" and "walking behavior". Walking ability is what a person is capable of doing and a person's walking ability is indicative of their quality of life as it is considered to being essential for most activities of daily living (Tudor-Locke 2001; Winter 2010). Strictly speaking, walking ability does not necessarily reflect actual habitual behaviors seen in normal daily life routines, i.e. walking behavior. Walking behavior is how a person normally walks in their daily life. For example, a person typically walks at a moderate pace to work and back home (walking behavior), but may be able to walk much faster or even run if motivational influences prompts them (walking ability).

Walking ability is multifactorial and encompasses endurance, speed, power, balance, and poise. It is well known that walking ability is not only affected by MS, hip fracture and sarcopenia, but is also modified by obesity, asthma, COPD, diabetes, heart insufficiency, hypertension, stroke, Parkinson's disease, Alzheimer's disease, and other neuromuscular and neurodegenerative diseases, as well as by aging and age-related frailty (WHO fact sheet 2016, WHO Recommendations 2010, Cesari 2011). For Parkinson's disease, e.g., difficulties in walking are among the first early symptoms that indicate the onset of disability (Shulman 2008). In Alzheimer's disease, gait speed declines before cognitive deficits become symptomatic (Verghese 2014). A person's walking ability determines their independence at home, capacity to achieve self-actualization and to function in society, and is therefore a clinically relevant target. However, a true and direct measurement of a patient's walking ability is difficult due to motivational factors, "white coat effect" and limited space and time during clinical interactions.

The limitations of current methodologies have motivated our efforts to find a pragmatic substitute for walking ability and to find or develop tools to measure it (Helmerhorst 2012). Such limitations include the inability of short-term clinical tests to assess true walking ability or capture fluctuations and exacerbations in performance, as well as self-reported activity questionnaires yielding incomplete, insensitive and/or variable results.

A pragmatic substitute for walking ability should:

1. Have an obvious link to a patient's quality of life.
2. Be quantifiable with current technology with sufficiently low signal-to-noise ratio to allow for manageable sample sizes.

Walking behavior fulfills the first requirement. In disabled patients, long-term real-world walking *behavior* is strongly linked to walking *ability*, since it can be expected that patients will frequently reach the limits of ability in daily life. For example, in the United States the ability to walk at least 1.32 m/s is considered to be the lower threshold for safe street crossing (Salbach 2013). We therefore consider real-world walking behavior, measured continuously, as a potentially reliable endpoint for use in clinical trials and as a reasonable surrogate to estimate a person's walking ability as well.

Walking behavior, in contrast to walking ability, has another substantial advantage: there is a strong body of evidence that walking is critical for a person's health. This notion is supported by epidemiological data and more recently by studies uncovering the molecular basis for the beneficial effect of walking exercise on muscles action via anti-inflammatory, neuroprotective and neurodegenerative qualities (Pedersen 2009, Handschin 2008, Safdar 2016). Therefore, actual walking behavior indicates the use of large muscle groups which is linked to the production of myokines and exerkines. Walking ability alone does not trigger this effect. Therefore, the link from actual walking behavior to a patient's quality of life is extending to the future.

A reliable quantification of real-world walking behavior can now be achieved using the actibelt. We are able to instruct patients to wear the device in their normal daily life routines to gather detailed recordings of their true daily walking behavior, thereby fulfilling the requirements formulated by Pearson et al (Pearson 2004) that a "gold standard" for measuring ambulatory mobility in neurological disorders should be the total ambulatory activity undertaken by an individual in their usual environment in performing their usual range of daily activities. From a patient's recordings, bouts of daily walking can be extracted and the corresponding durations, distances and speed can be measured. Other aspects linked to real-world walking behavior include gait variability, gait asymmetry, gait instability, including stumbling and falls, and the statistical distribution of sequences of steps in a row. Accurate estimates for the number of steps per day obviously need high daily wearing times; estimates for mean daily walking speed are more robust.

It is obvious that real-world walking speed, as element of real-world walking behavior is of particular importance and therefore is a valuable measurement from a clinical perspective in

patients with walking disturbances From an evolutionary perspective, inability to walk or run fast enough was linked to low fitness and survival (Bramble 2004; Lieberman 2015).

In summary real-world walking behavior as a multidimensional variable is a pragmatic substitute for walking ability, consisting of:

- The daily pattern of walking for an individual (e. g. walking in the home, walking the dog to the park and back twice a day 7x per week, walking to a shop and back 2x per week etc.),
- Quality of walking (gait variability, gait asymmetry, gait instability, including stumbling and falls), and
- The speed of walking during each of the specific walking bouts.

1.4 Summary of the actibelt® technology

The core of the actibelt technology is a 3D (tri-axial) accelerometer in a belt buckle, designed for unobtrusive long-term and continuous recording of acceleration data without need for recharging or other user interaction. Positioning the actibelt around the waist enables measurements to be taken close to the body's center of mass to retrieve information about walking behavior, in particular walking speed, more accurately than other types of mobility sensors that are worn on the wrist or ankle. Algorithms have been developed to compute certain aspects of walking behavior, for example, the number of steps and walking speed for each step. These algorithms and their correlation with actual speed have been repeatedly validated, both for MS patients in clinical environment (Motl 2012) and healthy individuals in daily life (Schimpl 2011a; Schimpl 2011b).

There are three main components of the actibelt technology:

i. actibelt recording box ("data logger") and accessories (further described in section 1.4.2) – This includes the device itself, accessories (e.g., belts) and the data management application (actibelt Manager App),

ii. Analysis algorithms (further described in section 1.4.3) – These are scientifically validated algorithms to analyse actibelt-generated data, and

iii. Data Warehouse (further described in section 1.4.4) – An accelerometry data warehouse located at Trium and SLCMSR established in 2006 to securely store data collected from actibelts, and which currently stores more than 100,000 measurement hours.

1.4.1 History of actibelt development

Since its inception, the actibelt has undergone several changes to upgrade on battery life, data storage capacity and improve user needs. The overall 3D accelerometry based technology has remained unchanged.

The first version of the actibelt, RCT0, was developed in 2005 and was used in several clinical studies and research projects including aerospace research and sports (the latter two areas are out of scope of this Briefing Book). This initial version was capable of 7 days of recording when the device was switched off during the night. The following version, the actibelt RCT1, was refined to have a smaller measurement unit, smaller buckle and longer battery life time to allow for up to 10 days of data storage. Again, the RCT1 was used as a research tool and was employed in large observational studies and clinical trials for exploratory endpoints measurements.

The current version of actibelt, RCT2, the focus of this Briefing Book, was introduced to meet the requirements of two Novartis phase 2 clinical trials in patients recovering from hip fracture and sarcopenia (www.clinicaltrials.gov - Identification Numbers NCT02152761 and NCT02333331, respectively, see Appendix D). For these trials, a battery life time of ≥ 4 weeks was required and a method to check if the belt was worn by the patient was integrated (a magnetic sensor in the recording box detects if the belt, that contains magnets at defined positions, is closed). The actibelt RCT2 version is now capable of 8 weeks of continuous recording, and a set of validated algorithms have been developed to extract parameters including step numbers and gait speed. The actibelt RCT2 has the necessary approval for use in clinical trials in the EU, USA, and Japan and has been certified according to UL 60950-1:2011, “Standard for Safety for Information Technology Equipment - Safety - Part 1: General Requirements” and is a consumer grade device.

To date, the various actibelt versions have been used for research in a wide area of clinical fields: neurology, musculoskeletal, cardiology as well as aerospace research. In addition, the device has also been integrated in a local trial in Germany (phase 4) to measure exploratory endpoints in COPD. The three Novartis sponsored trials are further described in Appendix D.

In 2007, the SLCMSR began creating the actibelt BLU version, a research platform using Bluetooth capability and various options for additional sensors such as atmospheric pressure, RFID, gyroscope, and compass. The actibelt BLU version will not be the focus of this Briefing Book, though potentially it may have future applications in research settings or in providing feedback to the wearer.

1.4.2 actibelt recording box and accessories

The actibelt's 3D accelerometer is enclosed in a battery powered recording box, which captures 3-dimensional acceleration (along the x, y and z axis) and belt closure state (open or close) at 100 Hz for up to 8 weeks of continuous recording. The recording box is produced in a controlled environment (factory inspections by a Notified Body), to be compliant with SGS safety mark. SGS North America is officially recognized by the Occupational Safety and Health Administration (OSHA), as a Nationally Recognized Testing Laboratory (NRTL) in the US and is accredited by the Standards Council of Canada (SCC).

The recording box is either mounted in a leather belt (typically preferred by men) or a flex belt (typically preferred by women), and both function to position the recording box concealed near the center of mass of the human body. The flex belt is worn typically over the underwear, not directly on the skin and underneath other clothing, whereas the leather belt acts as a common belt.

The main focus of the design of the device has been simplicity of use for patients paired with a sufficient number of choices (different types of leather, width, length) to best match the patient's individual style. There is minimal patient interaction with the device (e.g., no charging, no on/off switch, no starting/stopping, no configuration), other than closing the belt buckle and wearing the belt around their waist. This was achieved by using a battery efficient accelerometer sensor, as well as the inclusion of a belt closure recording mechanism to filter out non-wearing times. User acceptance and adherence by patients have shown to be generally high (Schlesinger 2011; Scheermesser 2008).

To support and manage the use of actibelt devices in clinical trials, an Android based application called the actibelt Manager App was developed for use by the healthcare provider. The actibelt Manager App enables three modes of operations:

- Handout – Preparation and configuration of a recording box prior to handing it out to a patient by the healthcare provider.
- Download – Downloading, compressing and encrypting data (both from clinical short tests and real-world walking behavior) from a recording box returned by the patient.
- Capturing short tests (optional feature) – Capturing timestamps in clinical short tests, e.g. gait, balance, dual tasking.

1.4.3 Analysis Algorithms

Various analysis algorithms have been developed over the past 10 years, focusing on extraction of timestamps of individual steps, time-varying gait-speed, falls and derived parameters (e.g., walking, step frequency per week, and others referenced in the table below).

Table 1-1 below summarizes parameters that can currently be extracted automatically from actibelt recordings**.**

Table 1-1 Summary of automated parameters to be extracted from actibelt recordings

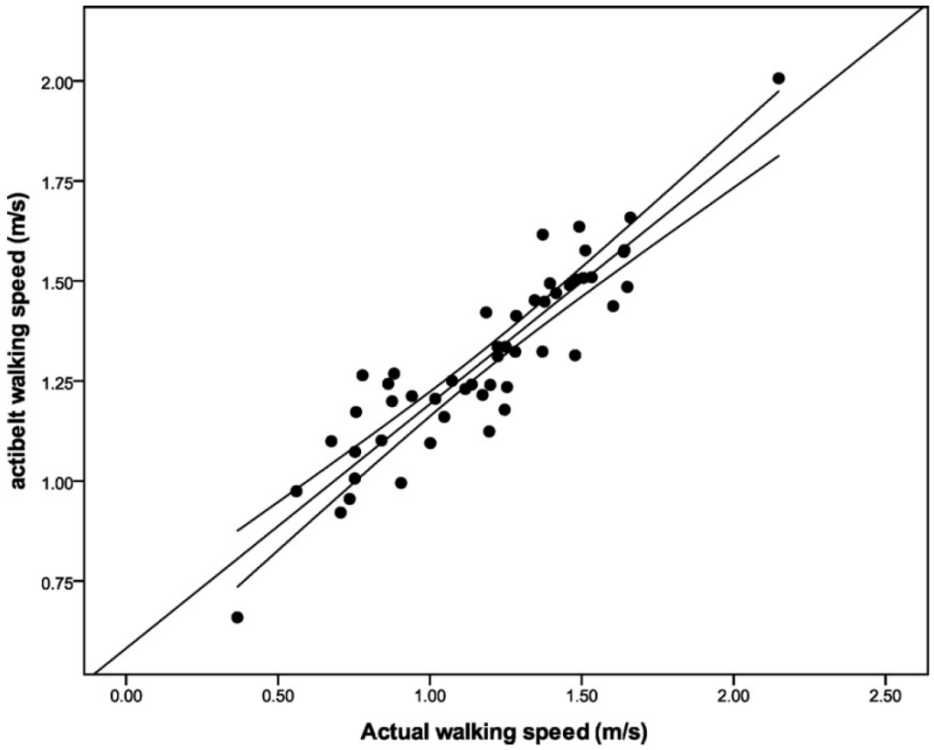
No.	Parameter	Unit Expected	Description	References
1	**Average time belt worn per week**	hours	Total amount of time the recording boxes were worn during the week calculated across days available for week (sum).	Derived from combining the information from Kraftschlussschalter (KSS) or so called magnetic switch that registers belt closure with a merging algorithm that takes into account the accelerometer data..
2	**Steps walking per week**	-	Total number of steps the subject walked during the week calculated across days available for week (sum).	Derived from [Daumer 2011], [Schimpl 2011a], [Motl 2012], [Schimpl 2011b],[Franzelin 2009], [Lederer 2009], [Schimpl 2011c], construct validity via [Schimpl 2011b]
3	**Walking step frequency per week**	per min	Average daily walking step frequency of subject calculated across days available for week (average).	Derived from [Schimpl 2011a], construct validity via [Schimpl 2011b]
4	**Total walking time per week**	hours	Total time the subject spent walking during the week calculated across days available for week (sum).	Derived from [Schimpl 2011a], construct validity via [Schimpl 2011b]
5	**Total distance traveled per week**	m	Total distance the subject covered while walking and running during the week calculated across days available for week (sum).	Derived from [Soaz 2012b] (strictly speaking from the variable speed per step), construct validity via [Schimpl 2011b]
6	**Mean velocity while walking / real-world walking speed per week**	m / sec	Average daily walking speed of subject calculated across days available for week (average).	Derived from [Schimpl 2011a], [Motl 2012], [Schimpl 2010] construct validity via [Schimpl 2011b]
7	**Maximum coherent walking distance per week**	m	The maximum uninterrupted distance the subject covered in one bout during the week calculated across days available for week (maximum)	Derived from [Schimpl 2011a] (strictly speaking from the variable step detector), construct validity via [Schimpl 2011b]
8	**Steps running per week**	-	Total number of steps the subject ran during the week calculated across days available for week (sum).	Based on distinction of running from walking, construct validity
9	**Total running time per week**	hours	Total time the subject spent running during the week calculated across days available for week (sum).	Based on distinction of running and walking, construct validity

No.	Parameter	Unit Expected	Description	References
10	**Ratio of steps within sequences of 50 or more steps per week**	-	Average daily fraction of steps which were walked in bouts of at least 50 consecutive steps calculated across days available for week (average)	Derived from [Schimpl 2011a] (strictly speaking from the variable step), construct validity via [Schimpl 2011b]
11	**Mediolateral body sway test**	m / sec^2	Standard deviation of mediolateral sway based on acceleration	Derived from [Soaz 2011], [Soaz 2013]
12	**Fall detection**	-	Detection of fall based on acceleration and tilt angle.	Derived from [Soaz 2012a], [Soaz 2012b], [Iovkova 2010]

min = minute; m = meter; sec = second

These algorithms and their correlation with actual speed have been repeatedly validated, both for MS patients in clinical environment (Motl 2012) and healthy individuals in daily life (Schimpl 2011a; Schimpl 2011b). Improving the walking speed algorithms accuracy for sarcopenia and hip fracture recovery is currently in progress in collaboration with Novartis. In Figure 1-1 below, Motl et al. showed that, in 51 patients with MS scoring between 2.0-6.5 on the EDSS scale, there is a strong association between actual walking speed measured by the 6 Minute Walk Test (6MWT) and walking speed measured by the actibelt. However, for the entire group of MS patients, it was shown that the actibelt overestimated walking speed (calculated as actual speed minus actibelt speed) by -0.12 ± 0.17 m/s ($p < 0.0001$). When the MS patients were stratified into mild, moderate and severe groups, it was shown that no significant overestimation in walking speed was observed for mild MS (-0.2 ± 0.12 m/s). Overestimation was seen in both the moderate and severe MS populations (-0.10 ± 0.16 m/s and -0.26 ± 0.12 m/s, respectively). Such an overestimation is a result of the algorithms that were developed based on healthy individuals.

Figure 1-1 **Extracted from [Motl 2012], "Scatter plot along with line of best fit and 95% confidence limits for the association between gold standard 6MWT speed (distance walked in 6 minutes divided by 6 minutes) and walking speed calculated from actibelt measurements (without knowing the distance) for a group of MS patients". Note that the diagonal line is not the bisecting line.**



We expect that with our ongoing refinement and validation process which includes more data from elderly individuals and from patients with severe walking impairment, bias as well as variability can be further reduced as needed for specific patient populations. Currently Trium and SLCMSR are involved in two studies in partnership with LMU to study frail geriatric patients with impaired mobility (Ethics approval is underway) and patients with dizziness and vertigo (study collection from 60 individuals completed (Speed Validation Preprint). Data from the data warehouse will also be used, in particular gold standard data (high resolution videos) from the walking performance of elderly individuals as part of the refinement and validation process.

1.4.4 Data warehouse

Trium and SLCMSR have built an accelerometry data warehouse which currently stores more than 100,000 measurement hours and metadata collected by the actibelt from both healthy

subjects as well as patients with acute or chronic diseases. Sampling frequency, sensor type and sensor positioning have not changed over the years, allowing re-analysis of historical data (Soaz 2012a).

Since 2006, the team has built a data collection of more than 50 patient years of continuous monitoring of patients wearing the actibelt, including: MS, COPD, hip fracture recovery, sarcopenia, depression, schizophrenia, lupus, vertigo, knee injury, diabetes, as well as measurements from aerospace research and sports. Regions and countries where patient data were collected from includes EU, US, Canada, Japan, South America and Kenya.

1.5 Regulatory history

Trium and SLCMSR's history of interacting with regulators, academic institutions and commercial entities to discuss mobility as a valid endpoint for MS and other relevant diseases as well as to provide feedback and opinions on key initiatives in the field of mobility is summarized in Table 1-2.

Table 1-2 Trium/SLCRSR external interactions with regulators, academic institutions and commercial entities

Date	Document (* denotes document on file at Trium/SLCMSR)	Organization	Purpose/Conclusions/Summary
November 6, 2002	SLCMSR/Trium held meeting with FDA in Washington D.C., with Dr. Robert O'Neill, SLCMSR Minutes*	FDA	Purpose: Present goals/data/projects of SLCMSR. Discussing natural history data, design for phase 2 trials, statistical modeling, comparison group, surrogate variables, simulation of clinical trials Conclusion: SLCMSR/Trium was invited to send updates. Encouragement to use individual patient data collections for safety and outcome research.
August 11, 2004	SLCMSR Letter to FDA for the Critical Path initiative*	FDA	Purpose: Provided follow-up information regarding he database established by SLCMSR which contained clinical information about multiple sclerosis patients that can be used for improving clinical trials and better patient care. The Critical Path Opportunities Report from can be found here: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM077254.pdf
September 9, 2004	SLCMSR held meeting with EMEAs Efficacy Working party in London, Mutually agreed minutes*	EMEA	Purpose: discuss concept, achievements, design, and planned future activities of the SLCMSR from a regulator's perspective

Date	Document (* denotes document on file at Trium/SLCMSR)	Organization	Purpose/Conclusions/Summary
February 21, 2005	Letter to EMA *	EMA	Purpose: SLCMSR/Trium was invited to contribute to the preparation of the draft for MS guidelines CPMP/EWP/561/98 (found here: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003486.pdf). The following topics were presented: • Historical data sets for sample size calculation • Clarification of benefit of early treatment • Innovation with regard to placebo controlled trial design • Need for surrogate outcomes • Innovation in statistical analysis • Refining patient selection and stratification • Detecting "improvement" • Development of biomarkers
March 2006	Critical Path Opportunities Report (see pages R27, R28)	FDA	MS/SLCMSR listed as an example for a coordinated collaborative platform to attack a specific illness. The following topics were presented: • Using models to help identify the factors associated with the "point of change" in MS, at which an individual's disease changes from an intermittent to a chronic condition. • Developing new study designs for all phases of clinical research. • Evaluating the use of MRI imaging to assess disease status The Critical Path Opportunities Report can be found here: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM077254.pdf
December 7, 2007	International Physical Activity Expert Panel meeting	Organized by Trium, SLCMSR, Robert Bosch GmbH	Potential of Mobile Monitoring of Physical Activity to Improve Human Health: Results of an International Expert Panel Workshop. The workshop focused on discussion the current problems in monitoring the long-term evolution of disability – an essential element for assessing the long-term effect of drug treatments e. g. in MS and Parkinson's disease. Participants agreed that an easy-to-use system like the actibelt® could improve outcome assessments. The results of the workshop and the full list of members of the physical activity expert panel (including Novartis) can be found here: http://www.actibelt.com/2008_04_24_Poster_ICAMPAM_2_cmyk.pdf
July 2008	External review meeting "Towards the human motion project"*	University of Oxford	External review report by Rodney Philips, dean of the Medical Faculty of Oxford University, based on a site visit and report of the clinical research activities of SLCMSR/Trium and partners from LMU, TUM, Mayo Clinic, as well as Novartis.

Date	Document (* denotes document on file at Trium/SLCMSR)	Organization	Purpose/Conclusions/Summary
October 27-29, 2010	Acceleromics meets genomics – Höhenried	SLCMSR/Trium, University of Cambridge, LMU, TUM	Poster that summarizes the outcome of the workshop: http://www.actibelt.com/acceleromics_meets_genomics_poster.pdf
July 1, 2011, July 11, 2011, September 15, 2011	Letters* – in the context of conditional approval of Fampridine (See publications by [Schimpl 2011a]; [Motl 2012])	EMA	Submitted information about a new method (accelerometry) that may be of importance in trials that aim to show improvements on a broader primary endpoint that is clinically meaningful in terms of walking ability, and may also be used to objectively identify early on responders/nonresponders to treatment.
Since 2011	ENCePP membership (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance)	EMA	Trium also participated in Working group on Health Technology Assessment (HTA) and a Working group on Methodological Standards. Information on these initiatives can be found below: http://www.encepp.eu/events/documents/ENCePP_ISPOR_Poster_Nov2013_FINAL.pdf http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideMethStandardsPE_Rev3_Authors.pdf
Since 2011	Updates/phone calls/informal meetings during ENCePP sessions with EMA.		
July 25-26, 2011	Transatlantic Workshop PML	EMA, FDA	http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500111562.pdf
January 20, 2012	Letter to chairman CNSWP/EMA (with University of Oxford)	EMA	Invited summary of achievements & recommendations: e.g. future measures of mobility should include ecologically valid measurements for distance and speed, mobile accelerometry, access to raw data. Commented on draft MS guidelines.
July 27, 2012	Ensuring safe and effective medicines for an ageing population	EMA workshop	Invited participant. Steinhagen Thyssen/Charite presented to power of mobile accelerometry (actibelt was later used in Berliner Altersstudie BASE II study).
March 22-23, 2012	EMA geriatrics workshop	EMA Workshop	"Gait speed is a vital sign that needs to be measured in every study" (GlaxoSmithKline representative) http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/08/WC500131045.pdf
October 17, 2013	Workshop on the clinical investigation of new medicines for the treatment of multiple sclerosis	EMA	Summary of the Workshop: • Contribution to "setting the stage" presentation by G. Ebers • Deficiencies of currently used outcome measures were presented. • Difficulties of clinical short term tests highlighted by regulators. • Final result of open discussion: MRI should not be accepted as phase 3 endpoint. • The idea that mobile sensors and algorithms may be seen

Date	Document (* denotes document on file at Trium/SLCMSR)	Organization	Purpose/Conclusions/Summary
			as an "automatic PRO" was suggested. Link to the Workshop videos: http://www.youtube.com/watch?feature=player_embedded&list=PL7K5dNgKnawbBBGvQ-wEKZDhn87PJ975N&v=UhxPaLPKwxQ Link to the Workshop documents: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/06/event_detail_000724.jsp&mid=WC0b01ac058004d5c3#media
February 5, 2014	1st Winter Symposium of The Human Motion Project	SLCMSR/Trium, LMU, TUM, ETH	Accelerometry in sports, clinical trials and fall detection/prevention http://www.thehumanmotioninstitute.org/node/177
March 6, 2015	2nd Winter Symposium of The Human Motion Project	Contribution by BfArM, SLCMSR/Trium, LMU, TUM, DLR, ETH/Novartis	From gait labs to the real world: See "Regulator's view on the scientific and regulatory challenges in new mobility outcomes & PROs", found here: https://peerj.com/preprints/1270/ Symposium flyer can be found here: http://www.thehumanmotioninstitute.org/node/195
March 11, 2016	3rd Winter Symposium of The Human Motion Project "Is walking really medicine?"	Contribution by BfArM, SLCMSR/Trium, LMU, TUM, DLR, Novartis	Medical Device Safety: Investigating contributions of human factors ", found here: https://peerj.com/preprints/1840/ Symposium Flyer can be found here: http://www.thehumanmotioninstitute.org/node/211
July 22, 2016	Trium submits an application to the ITF to request a meeting	EMA ITF	Trium email EMA ITF with information package and preliminary questions that will be the eventual focus of the Briefing Book
August 17, 2016	Trium, with Novartis in attendance, held an initial conference call with ITF representatives regarding the meeting request and Briefing Book	EMA ITF	Trium, with Novartis in attendance, updated EMA ITF about current status of development and future plans. Input for preparation of briefing book.
November 11, 2016	Trium submits EMA ITF briefing book	Trium	Request for an ITF meeting
November 17, 2016	Feedback from EMA ITF – Ehmann Falk	EMA	Recommendation: "Having noticed how advanced your proposed technology is, the fact that multiple trials are ongoing using this technology and the nature of your proposed questions, we consider the best way forward for a continuous successful development to consult our colleagues in Scientific Advice / Qualification of novel methodologies team in CC.ITF discussions focus on methods, technologies and products in the concept stage which you passed.We hope you find this useful and are looking forward to a further successful implementation of your technology to finally the benefit of patients."

Date	Document (* denotes document on file at Trium/SLCMSR)	Organization	Purpose/Conclusions/Summary
January 24, 2017	Trium and Novartis held a Presubmission meeting with the EMA SAWP.*	Trium, Novartis, EMA	Clarify contents of the Briefing Book that was submitted on December 12, 2017. A presentation was given by Trium.
January 25, 2017	EMA SAWP issued meeting notes from the Presubmission meeting*	EMA	EMA emailed Trium "List of comments – Qualification Advice pre-submission meeting"
March 7, 2017	Expert panel meeting on wearables in clinical trials: Real-world walking speed as outcome	SLCMSR/Trium/TUM/LMU/University of Copenhagen/NIH	Planned outcome is a consensus document.
March 8, 2017	4th Winter Symposium of the Human Motion Project "Is gait speed a vital sign or a sign of vitality?"	SLCMSR/Trium, TUM, LMU, DLR	Planned outcomes are contributions from NIH, Mayo clinic, University of Copenhagen, DLR, TUM, LMU

1.6 Objectives of the EMA Qualification Procedure

The purpose of this EMA Qualification Procedure is to obtain advice and eventually receive an EMA qualification opinion on the acceptability of real-world walking speed as an aspect of real-world walking behavior, to be a primary endpoint in pivotal clinical trials in diseases where limited mobility forms the major burden for patients.

In the Day 60 meeting of the qualification procedure, Trium would like to obtain guidance from the EMA on the following topics:

- **Topics related to the endpoint definition**:
    - Question 1: Regulatory acceptance of real-world walking behavior as robust endpoint for mobility disorders
    - Question 2: Seven consecutive days of monitoring as a valid measurement duration
    - Question 3: Definition of clinically relevant change in real-world walking speed
    - Question 4: Real-world walking speed as outcome measures
- **Topics related to the device and methodology**:
    - Question 5: Device and algorithm qualification strategy
    - Question 6: Data quality
    - Question 7: EMA guidelines

2 Questions to the EMA

2.1 Endpoint Definition

2.1.1 Question 1: Regulatory acceptance of real-world walking behavior as robust endpoint for mobility disorders

Does the EMA concur that "real world walking behavior" is a relevant endpoint for regulatory decision making in diseases where limited mobility forms the major burden for patients, such as:

a) Multiple Sclerosis,

b) Recovery after surgical treatment of Hip Fracture,

c) Sarcopenia?

2.1.2 Trium Position – Question 1

It is well known in the literature and in the medical community that walking *ability* is clinically relevant for many types of diseases where mobility restriction or impairment is an issue (see for example (Del Din 2016) for Parkinson's disease). The limitations of currently used short term clinical tests to capture walking *ability*, include the inability to assess true walking ability or capture fluctuations and exacerbations in performance, as well as self-reported activity questionnaires yielding incomplete, insensitive and/or variable results. Long-term real-world walking *behavior* is strongly linked to walking *ability*, since it can be expected that disabled patients will frequently reach the limits of ability in daily life. Ability sets a ceiling on behavior, but more importantly, as ability declines, behavior declines even more as symptoms such as fatigue, shortness of breath, or dizziness limit behavior at a fraction of ability. Real-world *walking speed*, as element of real-world walking *behavior* is a particularly important parameter and is seen as a valuable clinical measurement in patients with walking disturbances. Not only is walking speed itself linked to mortality and falls in the elderly but habitual walking speed is sufficiently stable that it can be estimated with shorter observations than total walking activity (which requires continuous monitoring) (Studenski 2011).

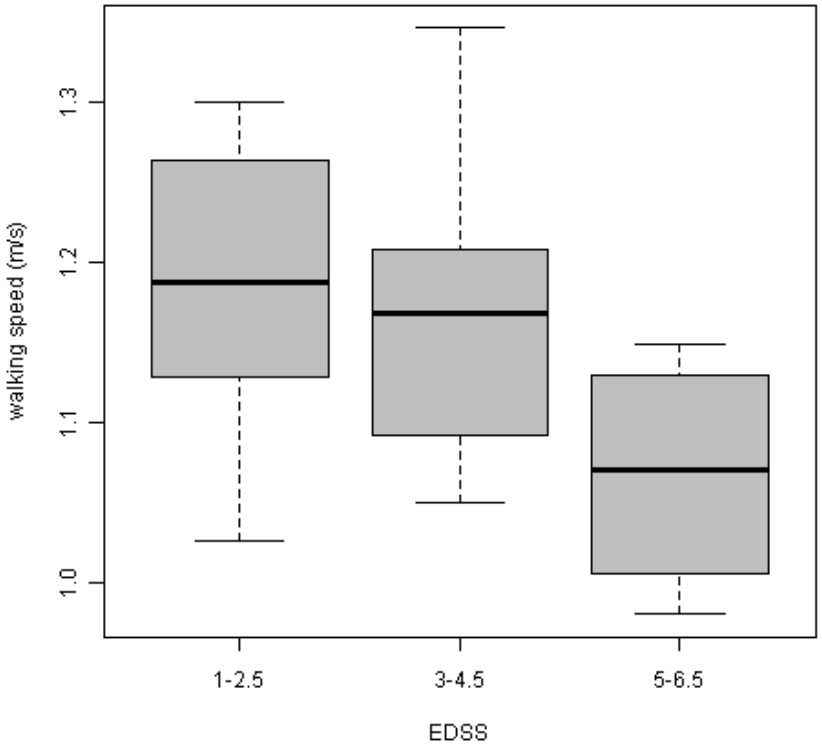
a) Multiple Sclerosis

In MS there is a special need for improved outcomes. When the SLCMSR was founded in 2001, it became possible to investigate the validity of endpoints based on pooled individual patient data (IPD). The currently accepted registration endpoint by major Health Authorities

for pivotal trials in MS is the "sustained progression" as measured by the Expanded Disability Status Scale (EDSS) and is defined by a rise in the EDSS score by 1.0 for at least 3 months (EMA Guideline). In an analysis performed by Ebers and Heigenhauser using the SLCMSR database with MS patient information, it was shown that for the most common type of MS, relapsing-remitting MS (RRMS), invalid outcome measures (or endpoints) based on EDSS were used for pivotal trials (Ebers 2008). Specifically, the study found that in placebo arms of RRMS clinical trials sequential EDSS measurements were not sensitive to detect changes even though one would expect a decline over time as the severity of the disease worsened. By definition, in the range used as an inclusion criterion for pivotal trials, EDSS is mainly based on walking distance. Even supposing that walking distance was measured correctly, it was shown that day-to-day variability of the measured walking distance of a subject reaches a value which is considered a clinically relevant change (up to 1.5 point change in EDSS) (Albrecht 2001). Therefore, EDSS has limitations and clear disadvantages. As mobility is a relevant readout for many disease indications beyond neurological disorders, we expect that efforts to validate other types of short-term surrogates to measure key outcomes would uncover similar challenges.

In a German multicenter study, 74 MS patients wore the actibelt for 7 consecutive days; it was demonstrated that a decrease in walking speed as measured by the actibelt correlated with increasing disability status using the EDSS scale as follows: 0.1 m/s decrease in real life walking speed corresponded to approximately 2 points on the EDSS in the critical range of EDDS = 3.0 – 6.5) as shown in Figure 2-2 below (IPAT 2012) (Appendix C). A confirmed 1.0 point increase in EDSS is currently an accepted endpoint for phase 3 studies in MS.

Figure 2-1 **Excerpt from IPAT2012, page 48: "Daily life walking speed differed between the disability subgroups (Kruskal Wallis test: p=0.0455). Patients with severe disability were slower than patient with mild or moderate disability. Median walking speeds were 1.19m/s (EDSS 1.0-2.5), 1.17m/s (EDSS 3.0-4.5) and 1.07m/s (EDSS 5.0-6.5)." Data represents a total of 74 relapsing remitting MS patients.**



b) Recovery after surgical treatment of hip fracture

Recovery of lower extremity function is the key determinant of overall function following recovery after surgical treatment of hip fracture. A majority of hip fracture patients report new limitations in lower extremity function that may persist up to two years post fracture (Magaziner 2000). In individuals recovering from hip fracture, gait speed is associated with quality of life, falls self-efficacy and depressive symptoms (Mangione 2007). In addition to these associations with clinical measures of gait speed, in the real world, gait speed is an important factor in determining an individual's ability to walk outside the home.

c) Sarcopenia

Sarcopenia may be considered both a process involving the loss of muscle with age, which happens universally, and an important cause of outcomes particularly in mobility disability and muscle weakness which happens in 2-4% of elderly people over age 65 (Studenski 2014).

For purposes of this Briefing Book and public health policy, we are interested in the latter. Slow gait speed is a key indicator of sarcopenia (Morley 2011), and is one of the most robust predictors of mortality, morbidity, and falls in the elderly. Sarcopenia and mobility disability are important disorders of the elderly, and are also intertwined with the geriatric syndrome of frailty, which may include other factors such as fatigue, weight loss, and other factors (Fried 2004). Frailty is out of scope for the current discussion.

We conclude that real-world walking behavior should be considered a relevant endpoint for regulatory decision making because of the following main reasons:

- Epidemiological data has demonstrated that physical activity inversely correlates with the progression of many chronic diseases. Improved measurement of activity can be expected to improve this correlation (Wareham 1998).
- Certain components of walking ability, have shown to be linked with mortality, quality of life (QoL) and health economics (Purser 2005; Hardy 2010; Studenski 2011) as summarized below:
    - Purser 2005: This study evaluated the usefulness of walking speed as an indicator of function and health status in acutely ill, hospitalized, older male veterans. Walking speed was derived from an element of the Reuben's Physical Performance Test (PPT), which includes a timed 50-foot walking test. It is assumed that this speed corresponds to the actual walking behavior in this group of individuals.
    - Hardy 2010: A study involving 5895 community-dwelling adults ≥65 years enrolled in Medicare demonstrated that the self-reported difficulty or inability to walk ¼ mile was associated with increased mortality (AOR (95% COI): 1.57 (1.10-2.24).
    - Studenski 2011: This study, based on a meta-analysis of 34,485 community-dwelling older adults aged 65 years or older, found that gait speed was associated with survival in all studies (pooled hazard ratio per 0.1 m/s, 0.88; 95% CI, 0.87-0.90; $P < 0.001$). Survival increased with increasing gait speed across the full range of gait speeds, with significant increments per 0.1 m/s.

2.1.3 Question 2: Seven consecutive days of monitoring as a valid measurement duration

Does the EMA agree that there is enough evidence available to support the use of real-world walking speed calculated as the mean of 7 consecutive days of monitoring in defining a valid endpoint for regulatory decision making?

2.1.4 Trium Position – Question 2

We have focused our research on walking speed, as one aspect of real-world walking behavior (full list of all aspects that can currently be measured can be found in Table 1.1) that holds the potential to characterize generally increasing frailty/ageing as well as clinically relevant transitions in disease where disability is a feature.

Our initial observations from real-world monitoring indicate that current standardized tests which capture walking speed (e.g., 6MWT and 400m WT) are not representative of daily life of a patient as they only provide a snap shot of a patient's mobility in a controlled clinic setting, hence we suggest to use real-world data captured using the actibelt to monitor patient-relevant outcomes.

We have used 7 consecutive days of monitoring to generate baseline data for calculating walking speed and subsequently, during a follow-up assessment, another 7 consecutive days of monitoring is generated. The change in the walking speed over the two time points is then calculated. A week-long of monitoring allows us to capture both weekday and weekend activities. The 7 days should ideally be representative for a "typical week" and not recorded for example, during a hiking vacation or before an exam where the patient has to study and remains sedentary. Either this effect needs to be treated as additional random noise, thereby increasing sample size, or it is handled by either checking special boundary conditions such as vacations before handout and/or record the information in the study CRF when the belts are returned. In the study by Schimpl et al (358 individuals), a strong association was found between mean 7 day consecutive real life walking speed and age (decrease of -0.037 m/s over ten years, $p < 0.005$) in healthy individuals wearing the actibelt (Schimpl 2011b). This was confirmed in an independent data set from healthy German individuals based on more than 500 individuals (Fasching 2014).

2.1.5 Question 3: Definition of clinically relevant change in real-world walking speed

We propose that 0.1 m/s (in other units 10 cm/s) should be a clinically relavant change in real-world walking speed, assuming seasonal effects can be controlled by study design in the following indications:

a) Multiple Sclerosis

b) Recovery after surgical treatment of Hip Fracture

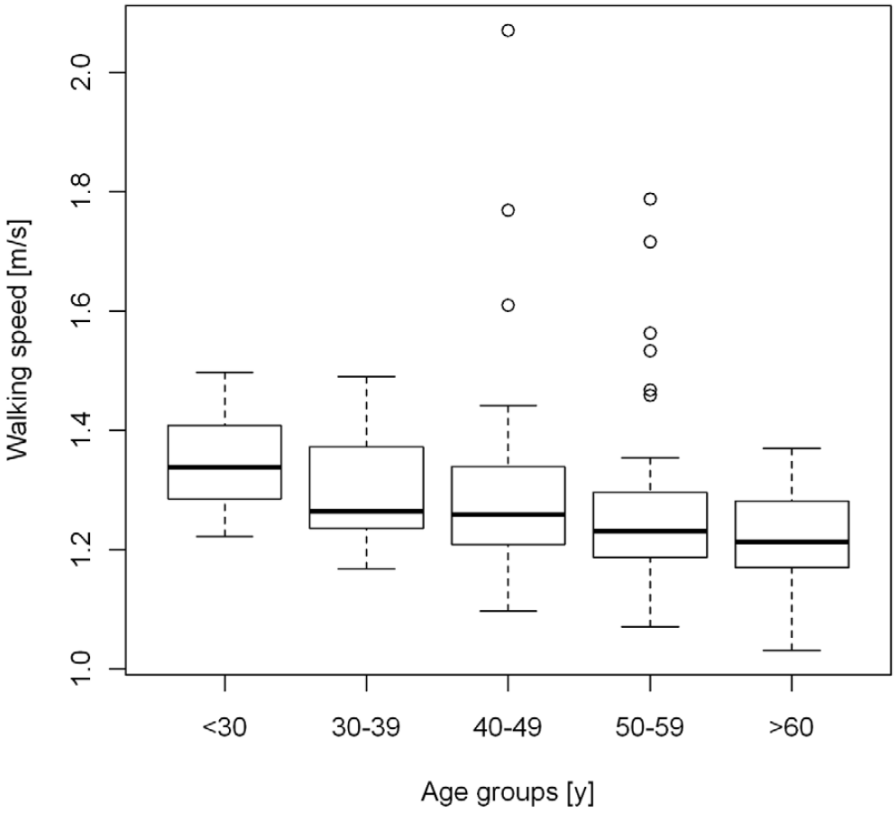
c) Sarcopenia

Does the EMA agree?

2.1.6 Trium Position – Question 3

We propose that in the majority of conditions a change in 0.1 m/s in real-world walking speed should be considered as clinically relevant. According to Schimpl et al, a decrease by 0.1 m/s corresponds to around 20-25 years of aging (average of 0.0037 m/s decrease of real-world walking speed per year) and a decrease in 0.05 m/s corresponds to more than 10 years of normal aging (Schimpl 2011b). Figure 2-1 below shows a significant decline in walking speed of 38 healthy individuals in the exploration and validation cohorts measured by the actibelt. A treatment effect corresponding to a difference in real life walking speed that is otherwise happening in 25 years should be considered a large effect, compared to the typical lifespan of an individual. Many diseases are considered to reflect “accelerated aging” in the sense that patients have functional capabilities that are reflective of older individuals.

Figure 2-2 Excerpt from [Schimpl 2011b]: "Boxplot showing the decline of real-world walking speed and age."



a) Multiple Sclerosis

From the IPAT study (see above) we know that a change of 0.1 m/s corresponds to a change of ≥ 2.0 points in EDSS, which is clinically relevant. Considering neurodegenerative diseases as a form of "accelerated aging", the correlation between age and walking speed in healthy subjects gives additional evidence.

b) Recovery after surgical treatment of Hip Fracture

In a study of 217 patients recovering from hip fracture, Alley and colleagues found that using both anchor-based estimates as well as cut points derived from receiver operating characteristic (ROC) curve analysis a 0.10-m/s cut point could be considered a small meaningful change during hip fracture recovery (Alley 2011). Furthermore, because lower extremity function, including gait speed, generally improves during the course of recovery from a hip fracture, in this same publication, Alley and colleagues examined the difference in change in gait speed from 2 months to 12 months post fracture, between individuals who

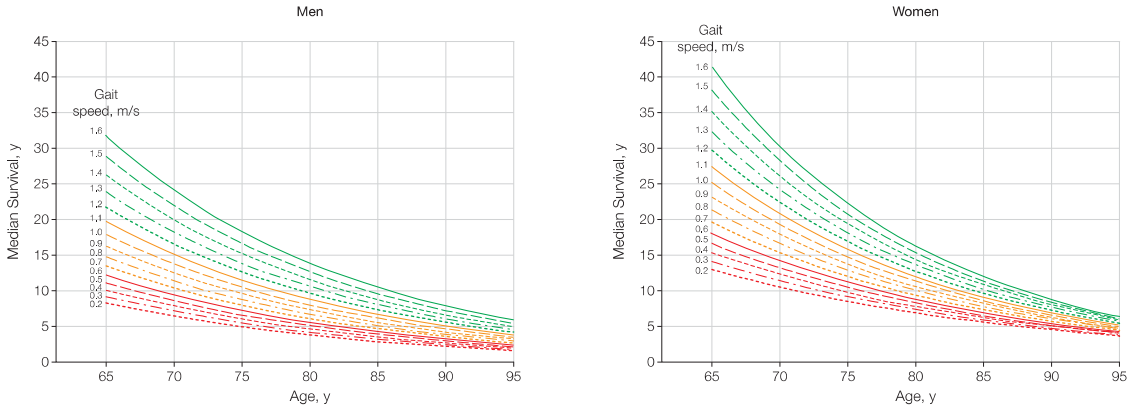
reported substantial improvement versus no change in their ability to walk one block. In these individuals the change in gait speed between 2 to 12 months 0.13 m/s (95% CI: (0.02–0.25), in individuals who reported substantial improvement versus no change over this time period.

c) Sarcopenia

As noted above, gait speed is a fundamental predictor of poor outcomes in geriatric populations. Over the past 15 years, evidence has mounted that a difference of 0.1 m/s (10 cm/s) is a relevant change in gait speed that is linked to change in risk of death, falls, hospitalizations, and healthcare costs (Purser 2005; Hardy 2010; Studenski 2011). In a study of function and health status in acutely ill, hospitalized, older male veterans, Pursel et al, concluded that "… each 0.10 m/s reduction in baseline walking speed was associated with poorer health status, poorer physical functioning, more disabilities, additional rehabilitation visits, increased medical-surgical visits, longer hospital stays, and higher costs. In addition, each 0.10 m/s/yr increase in walking speed resulted in improved health status, improved physical function, fewer basic disabilities, fewer instrumental disabilities, fewer hospitalization days and 1-year cost reductions of $1,188".

Another study involving 5895 community-dwelling adults ≥65 years enrolled in Medicare (Hardy 2010) demonstrated that the self-reported difficulty or inability to walk ¼ mile was associated with increased mortality (AOR (95% COI): 1.57 (1.10-2.24)). A more recent meta-analysis of 34,485 community-dwelling older adults aged 65 years or older, found that gait speed was associated with survival in all studies (pooled hazard ratio per 0.1 m/s, 0.88; 95% CI, 0.87-0.90; P < 0.001) (Studenski 2011). Survival increased with increasing gait speed across the full range of gait speeds, with significant increments per 0.1 m/s. (Figure 2-3):

Figure 2-3 Predicted median life expectancy by age and gait speed (Studenski 2011).



Based on these and other studies, we propose that 0.1 m/s (10 cm/s) is a relevant difference in gait speed, and that detection of this difference or change in a clinical trial is sufficient to claim a relevant impact on mobility in patients with sarcopenia.

In conclusion, we believe that a change in 0.1 m/s in real-world walking speed should be considered clinically relevant for MS, hip fracture and sarcopenia. This change in walking speed is supported by multiple studies from Studenski, Purser, Perera, and Hardy as described below:

- Data from Studenski show that a change of 0.1 m/s in gait speed should be considered a large effect size (0.05 m/s is small, but meaningful). However, the data are based on information collected mainly in a clinical setting (Studenski 2011).

- Purser et al demonstrated a predictive value of 0.1 m/s change in walking speed on various clinically relevant parameters (e.g., health status, physical functioning, disabilities, number of rehabilitation visits, number of medical-surgical visits, number of hospital stays, and medical costs). This study was based on in 1,388 acutely ill older male veteran patients recruited from 11 VA Medical Centers who were followed for one year (Purser, 2005). Walking speed was measured as usual walking speed in a clinical setting using the Reuben's Physical Performance Test which includes a timed 50 foot walk.

- Perera et al suggest in a study with 692 older adults (n=100 with mobility restrictions in a strength training trial, n=100 subacute stroke survivors and n=492 community-dwelling older people) to accept a small clinically meaningful change in usual walking speed (measured in a clinical setting by calculating distance walked divided by time where distances walked included 10 feet, 4 meters or 10 meters) near 0.05 m/s, and a substantial clinically meaningful change near 0.1 m/s. Both distribution based and anchor based methods were used (Perera 2006).

- Hardy, in a group of 439 older (>65 years) persons, showed that out of 6 measures only improved usual walking speed (usual walking pace over 4 m measured in a clinical setting) was associated with survival and predicted a substantial reduction in mortality. A consensus panel had defined the criterion for a clinically meaningful change in walking speed as 0.1 m/s beforehand, based on a literature review and clinical experience. The authors conclude that walking speed may be considered to be a "vital sign" for older adults (Hardy 2007).

Although arguments to use 0.1 m/s as a universal threshold exist, we believe that the difference of 0.1 m/s could be further reduced to 0.05 m/s for specific diseases where there is severe impairment (Bohannon 2014). As an example, supporting evidence for the 0.05 m/s value (or even 0.02 m/s) in Parkinson's disease comes from a study by Hass et al 2014 using data from >300 patients with Parkinson's disease (Hass 2014).

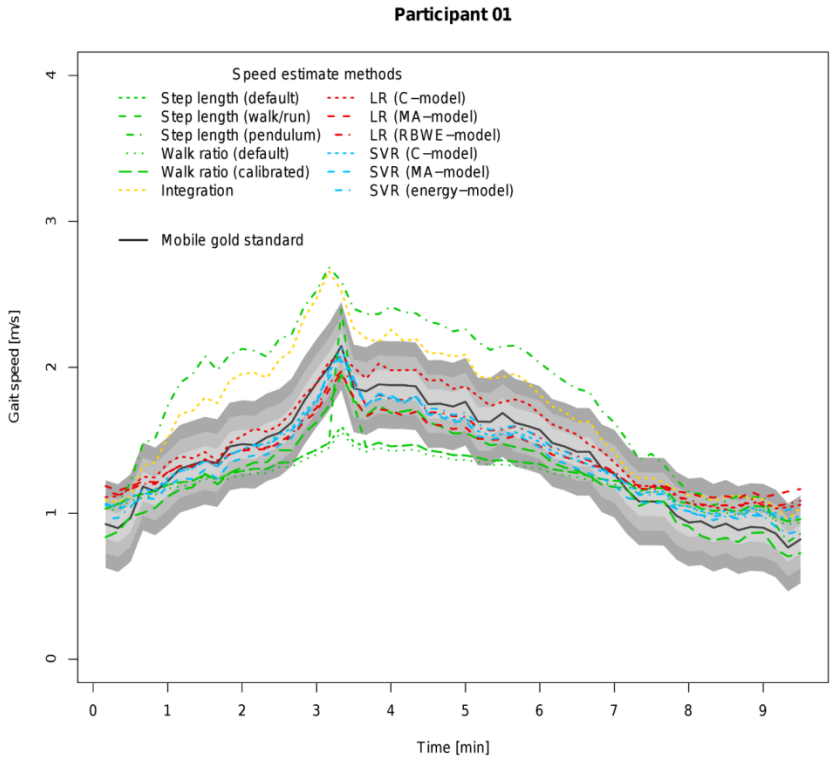
2.1.7 Question 4: Real-world walking speed as outcome measures

Does the EMA agree that the actibelt technology (including algorithms) is precise enough to detect clinically relevant changes in real-world walking speed?

2.1.8 Trium Position – Question 4

Gait speed assessment has been carefully developed, refined and evaluated using a strict validation policy (Daumer 2008; Schimpl 2011a). The current gold standard, using a measurement wheel and an electronic device to measure speed of the wheel, was developed for this purpose. The walking speed algorithm, based on support vector machine regression (SVR), was selected from a longer list of potential candidate algorithms. Its superiority and accuracy was confirmed in an independent data set, including data from outdoor measurements (see Figure 2-4).

Figure 2-4 **Excerpt from [Schimpl 2011a]: "Visualization of coverage probability for participant 01 (male, 46 years) in the experiment for outdoor ecological validity. The black solid line represents speed as measured by the mobile gold standard for running. Green, yellow, red and blue lines in different linestyles represent different speed estimates by different algorithms and models. The filled areas colored from light to dark grey around the black solid line indicate coverage probability levels from 0.1 to 0.3 m/s."**



Construct validity has been shown in a healthy UK population (n = 162 for validation data set, >300 individuals in total) (Schimpl 2011b). A linear decrease of real life walking speed could be shown (see Figure 2-2). This was confirmed in an independent data set from Germany (Fasching 2011).

A correlation between walking speed measured by the actibelt and walking speed measured in a clinical environment has been demonstrated in an MS population using a blinded split team approach (see Figure 1-1) (Motl 2012).

Several internal studies (sponsored by Trium/SLCMSR and Novartis) and studies with academic partners, in particular LMU Munich (Speed Validation Preprint) and DLR (Bedrest Preprint), are currently ongoing to further broaden the knowledge about the accuracy in different patient populations and conditions as well as in order to generate more gold standard data in "close to real world conditions" to be able to subsequently refine and validate the algorithms, if needed. We plan to consider patient's view during our development (Borup 2015).

2.2 Device and Methodology

2.2.1 Question 5: Device and algorithm qualification strategy

We would like to understand the EMA perspective of the following concepts:

a) Regulatory oversight of multi-component methodologies, specifically treatment of the measurement tool (e.g. actibelt) and separate decision algorithms for the purposes of medical device assessment and potential classification. Does the EMA agree that it is possible to formally "decouple" a data logging tool, like the actibelt, from associated algorithms which convert this raw data into interpretable information for decision making in pivotal trials?

b) Peer reviewed publications can form the basis for regulatory qualification of the algorithms, such that they can be used in pivotal trials to generate primary endpoint data. Does the EMA agree?

2.2.2 Trium Position – Question 5

a) We believe treating the actibelt and algorithms as separate entities, for the purposes of medical device assessment and potential classification would be the most logical approach to the development of these tools. With such an approach, the actibelt and the algorithm(s) could be verified and validated in a manner consistent with their classification, and their development cycles can be decoupled. The requirements for a data logging tool are to a large part independent from those of the algorithms and data management procedures that are used to extract information from the data. See MRI example below in response to part b.

b) By definition, publication in a peer-reviewed journal represents acceptance by experts in the field that the data and analysis presented meet the highest standards. It also indicates that the findings are an important contribution to the field, and allows the scientific community the opportunity to independently validate and improve the work.

There is precedence for such an approach. In MRI, the standard analysis packages (SPM, FSL) are not provided by the manufacturers of the machine, but by independent research groups who publish the algorithms using an open source license or a GNU General Public License such that the entire scientific community is part of the validation team. We plan to achieve a similar state of research and standardize open source algorithms in accelerometry analysis (Clay Preprint). This should stimulate innovation (e.g., additional parameters characterizing real-world walking behavior) and scientific rigor in the field (Ioannides 2005) by providing an open collaborative technology platform for the mobile medical monitoring of human motion (https://peerj.com/collections/6-humanmotionproject/).

2.2.3 Question 6: Data Quality

Does the EMA have any recommendations related to data collection and quality that are specific to continuous monitoring (e.g. risk for a patient not wearing the device themselves, but rather giving the device to another person)?

2.2.4 Trium Position – Question 6

Concerning data quality, there is a risk that the patient will give the device for example, to another person in order to avoid embarrassment that they are not performing well or to receive a given incentive. To de-risk this possibility, we suggest providing appropriate information about data flow and data usage to the patient and that no incentive should be given to the patient that is related to wear time or any outcome during the trial. These precautions should avoid motivating patients to "cheat" and artificially increase their wear time by handing over their belt to another person in phases of non-compliance, and also avoid introducing additional confounding factors relating to individual responses to that motivation (i.e. a subset of patients respond to the feedback, rather than the therapy tested, by increasing their activity).

Extended plausibility checks might be done using the raw data to determine whether the data pattern looks typical of the individual or not. Refining data checks is an option that Trium is currently evaluating. Although the analysis is performed with de-identified data, patients may feel uncomfortable with their data being checked for inaccuracies and thus may raise concerns with patient acceptance and data privacy.

2.2.5 Question 7: EMA Guidelines

Does the EMA foresee any change in EMA guidelines to include novel methodologies for capturing endpoints in clinical trials?

2.2.6 Trium Position – Question 7

Guidance on minimum standards for developing an accelerometry device for use in clinical trial (e.g. sampling rate, precision, wearing position) would stimulate manufacturer independent analysis software. We would be willing to support the regulators in these efforts through conferences, working groups or drafting of the guidance documents.

3 Appendices

3.1 Appendix A: Specifications for actibelt Recording Box Manager App

3.1.1 actibelt System

The actibelt system is an integrated platform to objectively assess the physical activity profile of a person using a high-tech 3D-accelerometer contained in a belt buckle. The actibelt records, from a position close to the body's center of mass, high-resolution (noise <0.01 g, 100Hz in three axis) long-term acceleration data. The core of the system forms an ultralow power 3-axis MEMS accelerometer that consumes less than 2 µA at a 100 Hz output data rate and 270 nA when in motion triggered wake-up mode. The orientation of the 3 orthogonal measurement axes allows observing the accelerations along the sagittal, longitudinal and transverse planes when worn in the belt buckle. These data are continuously read by an ultralow-power microcontroller. The architecture, combined with extensive low power modes, is optimized to achieve extended battery life in portable measurement applications. The device features a 16-bit RISC CPU and 16-bit registers. A digitally controlled oscillator (DCO) allows wake-up from low-power modes to active mode in 3.5 µs (typical). While in recording mode the data from the acceleration sensor is stored on an integrated 4 GB storage. In addition to these data, the binary signal of an integrated hall sensor is recorded. The value of this signal indicates the existence of a magnetic field near the recording box that is generated by a magnet at the opposite end of the belt. With this information the closed belt sequences can be identified which allows better adherence estimation. The time base of the recorded time-dependent 4 dimensional vector (3 acceleration axes and 1 binary signal from the hall sensor) is an integrated clock. In order to access the stored data, the device can change into a data mode that allows access to the encrypted files like on a USB mass storage device.

3.1.2 actibelt specifications

The actibelt unit is the equipment used by one trial subject during physical activity monitoring in the study. The actibelt unit components are: (1) actibelt recording boxes containing the 3D accelerometer where two are provided, (2) One flex belt and one common belt including white transportation boxes, and (3) carrying bag for transportation of the equipment and short instruction for trial subject.

Figure 3-1 actibelt unit components

Recording Box	
DIMENSIONS	68 x 39 x 11 mm
WEIGHT	50g
BATTERY	• Li-Ion • 3.7V • 1000mAh • 3.7Wh • more than 8 weeks continuous recording without recharging
CAPACITY	4GB
SENSORS	• 3D accelerometer • hall effect sensor (can detect belt removal)
ACCELEROMETER RANGE	+/- 6 *g*
ACCELEROMETER BANDWIDTH	4 m*g*
TIMING ACCURACY	10 ppm

Recording Box	
SAMPLING RATE OF SENSORS	100 Hz
INTERFACES	USB 2.0
Leather belt	
MATERIALS	• leather • polyamide • neodymium magnet • thread (100% polyester) • glue (polychloroprene, solvent-based)
LENGTH	80 – 120 cm
WIDTH	• 3.5 cm • 4 cm
COLOR	Black
Flex belt	
MATERIALS	• neoprene • artificial leather (free of AZO, Cd, FCKW, PCB, PCT, formaldehyde) • polyester • stainless steel • neodymium magnet • polypropylene • polyamide • acrylic glue • polyvinyl (cadmium-free) • nylon • iron (nickel-free) • thread (100% polyester) • glue (polychloroprene, solvent-based)
LENGTH	115 cm (adjustable)
WIDTH	4 cm

3.1.3 actibelt Manager App Specifications

The actibelt manager is used by the site. It is required for the administration of trial subjects and for the interim storage of their physical activity data synchronization of devices. The actibelt manager is composed of the following items: (1) customized touch tablet, (2) USB-OTG cable, (3) microSD card, (4) USB flash drive, (5) Bluetooth remote shutter, (6) USB charger for actibelt recording box, (7) AC power adapter for the touch tablet, and (8) actibelt data transfer log form, tablet unlock code and site manual.

Figure 3-2 actibelt Manager App components

OPERATING SYSTEM	Android™ 4.3
PROVIDED SOFTWARE	Human Motion Data Manager Instruction Video App
HOUSING	microSDHC™ , microSDXC™ (for data transmission)

3.2 Appendix B: actibelt Training Manuals and Videos

- Training videos:
  http://www.trium.de/download/ACT/Training_Actibelt_Suite_Webversion.mp4
- Video actibelt unit:
  http://www.trium.de/download/ACT/training_actibelt_unit_h264_1080p_v3_25042014.mp4
- actibelt site manual:
  actibelt suite - manual for clinical trials (actibelt site manual)

3.3 Appendix C: Integrated platform to quantify Physical Activity as outcome measure and Treatment option – IPAT

Joint SLCMSR e.V. & Trium project within "Competence Network Multiple Sclerosis"

Funding: Federal Ministry of Education and Research (01GI0920)

Duration: 01.06.2009 – 31.05.2012

Aim	Development and validation of an integrated discovery platform to handle –transmit, store, analyze and display – Physical activity (PA) data in the context of patients diseased with MS.
Hypothesis	We hypothesize that this study will confirm a significant and clinically meaningful association between "coherence length" and "active speed", i.e. two different measures obtained from accelerometric monitoring with the actibelt, with different categories of remitting or unremitting clinical disability (EDSS 1.0-2.5, EDSS 3.0-4.5, EDSS 5.0-6.5).
Population	MS patients (RRMS, SPMS, PPMS; EDSS 0 – 6.5), healthy controls
Data collected	n=340, 6659 measurement days (net measurement time> 10yrs)
Parameters extracted from recordings included (as of 2012)	• Activity counts (one mean filtered acceleration value per minute) • Activity regions (high, medium, low) • Activity temperature (mean activity per day) • Number of steps in any given period of time and distribution • Distance travelled and distribution • Gait speed • Gait asymmetry • Coherence length (measure for gait quality)

3.4 Appendix D: Novartis sponsored clinical trials utilizing the actibelt

Actibelt technology is currently successfully deployed in three randomized controlled trials (RCT) sponsored by Novartis, covering more than 50 sites across more than 10 countries. The three indications are in hip fracture, sarcopenia and COPD. In each case, actibelt was included as a basis for exploratory readouts, capturing real-world mobility parameters. Currently, data derived from actibelt are not used to provide evidence in the bimagrumab trials. A summary of the Novartis sponsored studies in hip fracture and sarcopenia presented

below. Although COPD is not an indication for which we are seeking qualification for currently, we have included information on this trial for disclosure purposes.

3.4.1 Summary (by trial)

	BYM338D2201	**BYM338E2202**	**CQVA149ADE05**
Demographics	>= 60 years, male and female	>= 70 years, community dwelling, male and female	>=40 years, European, community dwelling, male and female
Indication	Hip Fracture	Sarcopenia	COPD
Inclusion	- >= 60 years - Male or post-menopausal female - Hip fracture - > 35 kg bodyweight and 15-35 kg/m^2 BMI	- >= 70 years - Self-reported mobility limitations - 0.3m/s >= Gait speed over 4m <0.8m/s - <= 7.26 kg skeletal muscle/m^2 (men) - <= 5.5 kg skeletal muscle/m^2 (women) - > 40kg bodyweight and 18-30 kg/m^2 BMI	- >= 40 years - Stable COPD - <80% predicted FEV1 - >= 10 pack years smoking history RVol > 135% predicted
Exclusion	- History of fractures - Major mobility limitations - Conditions associated with muscle loss o Kidney disease o COPD o Hyper/hypo-thyroidism o Muscular dystrophies o RA o AIDS o T1D o Active GI disease - Liver conditions - Cardiovascular conditions - Drug use/abuse - Pregnancy/breast feeding	- History of fractures - PHQ-9 score >10 at screening - Comorbidities o Psychiatric disease o Ocular trauma o Neurological trauma - Conditions associated with muscle loss o Kidney disease o COPD o Hyper/hypo-thyroidism o Muscular dystrophies o RA o AIDS o T1D o GI disease - Liver conditions - Cardiovascular conditions - Drug use/abuse - Pregnancy/breast feeding	- Hypersensitivity to inhaled drugs - Long QT syndrome - Abnormal ECG/heart/cardiovascular abnormalities - Comorbidities o Asthma o Diabetes o Glaucoma o History of respiratory infection - Drug use/abuse - Pregnancy/breast feeding

N patients (target)	200	280	62
N patients (actibelt data collected as of Q4 2016)	14	29	0
Data availability	Blinded data on an ongoing basis	Blinded data on an ongoing basis, IA Q1 2018	Anonymized data as of Q2 2017
Length	24 weeks treatment + 24 weeks follow up	28 weeks	2 weeks treatment, 2 weeks washout, 2 weeks treatment, 4 weeks follow up
Description	A 24-week double blind treatment and 24-week follow up, randomized, multi-center, placebo-controlled, phase IIa/IIb study	A 28 week, randomized, double-blind, placebo-controlled, multi-center, parallel group dose range finding study	A randomized, blinded, double-dummy, single-center, placebo controlled, 2 period, cross-over study
Description of actibelt use	Patients were instructed to wear the belt for the whole duration of the trial to track physical activity (i.e., number of steps per minute, real-world gait speed, overall distance of walking, gait quality, and mediolateral body sway test). In addition, the actibelt is used for measuring duration spent while doing low, medium and high physical activity, falls and SPPB test.	Patients were instructed to wear the actibelt for four prescheduled periods of 5-6 consecutive days and should wear the device for a minimum of five continuous days at each assessment time point. The actibelt is used to monitor the patient's physical activity (i.e., number of steps, gait speed, distance walked, gait quality, different levels of physical activity intensity). Additionally, the actibelt is used to detect falls.	Patients were instructed to wear the actibelt for 7 weeks to monitor their physical activity (i.e., average number of steps at a given time/day).
Clinicaltrials.gov link	https://clinicaltrials.gov/ct2/show/NCT02152761	https://clinicaltrials.gov/ct2/show/NCT02333331	https://clinicaltrials.gov/ct2/show/NCT02442206

3.4.2 Performance measures (by trial)

Test group	Test element	BYM338D2201	BYM338E2202	CQVA149ADE05
6 minute walk test (6MWT)			X	
400m walk test			X	
Short Physical Performance Battery (SPPB)	Balance	X	X	
	4 m gait	X	X	
	5 times chair rise	X	X	
Hand grip test			X	

3.4.3 PROs (by trial)

Test group	Test element	BYM338D2201	BYM338E2202	CQVA149ADE05
Parker Mobility Questionnaire	Ability to get about the house	X		
	Ability to leave the house	X		
	Ability to go shopping	X		
SF-36			X	
EQ-5D-5L	mobility	X	X	
	Self-care	X	X	
	Usual activity	X	X	
	Pain/discomfort	X	X	
	Anxiety/depression	X	X	
	Global QoL	X	X	

General Mobility assessment	Ability to climb stairs	X		
	Ability to walk 2 blocks / 400m	X		
WHO global physical activity questionaire	Activity at work		X	
	Travelling to and from places		X	
	Recreational activity		X	
PHQ-9			X (at screening only)	
Mini Mental State Examination			X	
SAE/AE reporting	General	X	X	X
	Falls	X		

3.4.4 Actibelt (all trials)

Category	Readout	Unit	Sampling Rate
Aggregated activity parameter	Average time belt worn	Hours	1/week
Aggregated activity parameter	Steps walking	steps	1/week
Aggregated activity parameter	Step frequency walking	Steps/min	1/week
Aggregated activity parameter	Total time walking	hours	1/week
Aggregated activity parameter	Total distance walking	m	1/week

Aggregated activity parameter	Mean gait speed	m/sec	1/week
Aggregated activity parameter	Maximum coherent walking distance	m	1/week
Aggregated activity parameter	Steps running	steps	1/week
Aggregated activity parameter	Total time running	Hours	1/week
Aggregated activity parameter	Step ratio (walking bouts of more than 50 steps as a fraction of total walking bouts)		1/week
Balance test	Mediolateral sway	m/sec^2	1/month
Raw data	3D accelerometry	G	100/second

3.4.5 Analysis overview (for hip fracture and sarcopenia):

- **Validation of accuracy/sensitivity**
  - Collection of, and comparison to, "gold standard" (video and highly annotated ground-truth) data in target demographics
    - Demonstrate that gait speed algorithm (including step detection) is accurate (compared to clinical standards such as the 6MWT) and reliable, under semi-controlled conditions, in indications that may include pathological or asymmetric gait phenotypes
  - Head-to-head comparison of data collected during clinically accepted standardized functional gait tests (6MWT, etc.), focusing on step detection and gait speed estimation
    - Compare performance (variability and change over time) captured by standardized, HA accepted tests (e.g., SPPB) versus real-world actibelt parameters
  - Assessment of how wear time influences stability of key actibelt readouts
    - Assess if 1 week of data collection in real-world, clinical trial (non-volunteer) situations conditions is sufficient for a reliable readout

- **Definition and validation of clinically meaningful change**
    - Comparison to primary outcomes (e.g., SPPB for Sarcopenia)
        - Assessment of changes observed in real-world actibelt parameters versus functional primary outcomes (intra-patient changes over time and inter-patient between groups reporting improvement/decline)
    - Comparison to PRO
        - Assessment of changes observed in real-world actibelt parameters versus subjective primary outcomes (intra-patient changes over time and inter-patient between groups reporting improvement/decline)

3.5 Appendix E: 3D accelerometry based devices marketed as consumer grade product or with regulatory approval

Device Name (Manufacturer)	US Regulatory Status	EU Regulatory Status	Description and Uses (from manufacturer's website)	Phase 3 Clinical Trials*
MoveMonitor, also called DynaPort, DynaPortMM, DynaPortMT (McRoberts B.V.)	510(k) exempt, Class II device, Registered and Listed	"EMA Approved" stated on website. It is unclear whether this implies CE Marking to the Medical Devices Directive.	The device is worn in an elastic strap on the lower back to measure a patients' physical activity for up to 14 days. The MoveMonitor system consists of a hardware unit, managing software, and one or more chosen analysis modules, accessible through the manufacturer's web service.	One Phase 3 trial identified: • Study title: BACE Trial Substudy 1 - Physical Activity as a Crucial Patient Reported Outcome in COPD. Dynaport used to measure a primary outcome (number or steps taken by COPD patients). Identifier #NCT02205242.
Actigraph GT3X+ (ActiGraph Corp)	510(k) K080545, Class II device	Class I device, CE Marked	The GT3X+ based activity monitors provide objective measurements of human activity and are used in many research and clinical applications. They include both a micro-electro-mechanical system (MEMS) based accelerometer and an ambient light sensor. The GT3X+ can also be ordered with a wireless option, wGT3X+,	One Phase 3 trial identified: • Study title: Facilitating an Exercise Habit Via the Multi-Process Action Control Model: A Randomized-Controlled Trial. Actigraph GT3X used to measure a primary outcome (physical activity over a week). Identifier #NCT02785107.

Device Name (Manufacturer)	US Regulatory Status	EU Regulatory Status	Description and Uses (from manufacturer's website)	Phase 3 Clinical Trials*
			further extending the capabilities of the device.	
RT6 Accelerometer (Stayhealthy, Inc.)	US: For research use only	Not a medical device	The device measures activity in kinematic (raw data) or kcal (calorie expenditure) mode, tracking both acceleration and angular rate. The device includes 6 sensor technology (triaxial accelerometer and triaxial gyroscope) that records real-time energy expenditure.	No Phase 3 trials listed
Nike Fuelband (Nike)	Not a medical device	Not a medical device	The device measures everyday activity and turns it into NikeFuel. NikeFuel reflects the level of effort throughout the day. It's calculated the same way for everyone, so you can compare and compete with friends and other Nike+ members.	No Phase 3 trials listed
Fitbit ChargeHR and Fitbit Flex	Not a medical device	Not a medical device	Fitbit ChargeHR: Make every beat count with Charge HR™—an advanced tracking wristband that gives	One Phase 3 trial identified for Fitbit Charge HR: • Study title: A Pragmatic, Phase III, Multi-site, Double-blind, Placebo Controlled, Parallel Arm, Dose Increment

Device Name (Manufacturer)	US Regulatory Status	EU Regulatory Status	Description and Uses (from manufacturer's website)	Phase 3 Clinical Trials*
			you automatic, continuous heart rate and activity tracking right on your wrist—all day, during workouts and beyond. Fitbit Flex: Your Flex uses a MEMS 3-axis accelerometer that measures your motion patterns to determine your calories burned, distance traveled, steps taken, and sleep quality. Flex also contains a vibration motor, which allows it to vibrate when alarms go off.	Randomised Trial of Regular, Low Dose Extended Release Morphine for Chronic Refractory Breathlessness. Fitbit ChargeHR used to measure primary outcome (number of steps per day). Identifier # NCT02720822. Two Phase 3 trials identified for Fitbit Flex: • Study title: Family-based Approach in a Minority Community Integrating Systems-Biology for Promotion of Health. Fitbit Flex used to generally track physical activity associated with lifestyle counseling. Identifier #NCT02481401. • Study title: Lupus Intervention for Fatigue Trial. Fitbit Flex used to generally monitor physical activity associated with coaching sessions. Identifier # NCT02653287. One Fitbit (model unknown) Phase 3 trial identified: • Study title: A Randomized, Double-blind Placebo-controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness. Fitbit (model unknown) used to measure secondary

Device Name (Manufacturer)	US Regulatory Status	EU Regulatory Status	Description and Uses (from manufacturer's website)	Phase 3 Clinical Trials*
				outcome (activity and inactivity periods). Identifier # NCT02865460

* The website www.clinicaltrials.gov was accessed in November 2016. The advanced search function was used to identify "Phase 3" trials.

3.6 List of other Appendices

[Appendix F]Actibelt Site Manual (English, Version 1.4)

[Appendix G] Memo Actibelt Product Classification for Study Submission (April 9, 2014)*

*Note that the attachments to the memo (CB Report Certificate IEC 60950-1, USTC listing certificate for US and Canada, FCC Report, Label specification) can be provided upon request.

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