The Lokomat® Robotic in Mobility-Dependent Adult Patients with Subacute Stroke: Cardiovascular Exercise and Transition to Body-Weight Supported Treadmill Training.

by

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ABBREVIATIONS

ADL	Activities of Daily Living
AIHW	Australian Institute of Health and Welfare
APF	Augmented Performance Feedback
AROC	Australasian Rehabilitation Outcomes Centre
ASIA	American Spinal Injury Association
BORG-D	BORG-Dyspnoea
BORG-L	BORG-Leg
BWS	Body Weight Support
BWSTT	Body-weight Supported Treadmill Training
CPET	Cardiopulmonary Exercise Test
CR-10	Category Ratio 10 (Rate of Perceived Exertion Scale)
CV	Cardiovascular
EMG	Electromyography
FAC	Functional Ambulation Category
FC-RATE	Feedback Controlled Robotic Assisted Treadmill Exercise
FES	Functional Electrical Stimulation
FITT	Frequency, Intensity, Type, Time
GF	Guidance Force
GT	Gait Trainer
HR	Heart Rate
HRR	Heart Rate Reserve
LEMS	Lower Extremity Motor Score

MET	Metabolic Equivalent of Task
MMSE	Mini Mental State Examination
RPE	Rate of Perceived Exertion
SALL	Standing Affected-Leg Lift
SCATS	Spinal Cord Assessment Tool for Spasticity
SCI	Spinal Cord Injury
TUG	Timed Up and Go
VO_2	Oxygen Consumption
VO_2max	Maximum Oxygen Consumption
WISCI II	Walking Index for Spinal Cord Injury 2
WIT	Weighted (sum of) Interaction Torques

SUMMARY

Stroke precedes low cardiovascular (CV) fitness, prompting national guidelines (Stroke Foundation, 2017) to recommend that subacute stroke rehabilitation include a minimum of 30 minutes of moderate intensity CV exercise, measured as 40-60% maximal oxygen consumption (VO_2max), 3-6 Metabolic Equivalent of Task (MET), or 3-4 on the category ratio (CR-10) BORG scale (American College of Sports Medicine, 2014). Suboptimal levels of CV intensity are continually reported on the Lokomat® (Lefeber, Swinnen, & Kerckhofs, 2016) however, the Augmented Performance Feedback (APF) activities, which may assist in increasing CV workload (Koenig et al., 2011), have not been studied. Conversely, Body-Weight Supported Treadmill Training (BWSTT) has demonstrated efficacy for CV training in subacute stroke (Mackay-Lyons, McDonald, Matheson, Eskes, & Klus, 2013). Nonetheless, parameters to guide clinical decision-making regarding transition from the Lokomat® to BWSTT in stroke are unknown. As such, for mobility-dependent patients with subacute stroke, the primary aims of the current research were: (1) to determine if sustained moderate intensity CV exercise could be achieved using the APF activities of the Lokomat®; and (2) to explore the development of an algorithm and propose a clinical decision-making tool guiding transition from the Lokomat® to BWSTT in stroke.

Two observational studies were completed using 10 adult subacute rehabilitation inpatients with stroke. The first study assessed the CV workload achieved during three APF activities (Faster, Graph, Gabarello 2). CV workload was measured objectively by oxygen consumption (VO_2) and MET, and subjectively by the BORG rate of perceived exertion (RPE) CR-10 scale for both breathing and affected-leg effort. Participants also rated their motivation and enjoyment, and Lokomat® settings were recorded. In the second study, an algorithm and clinical decision-making tool were proposed based on comparison of outcomes between participants clinically judged as ready versus not-ready for BWSTT. Outcomes measured for comparison included the: Functional Ambulation Category (FAC) score; assistance required for sit to stand, standing balance and evenness of weight-bearing; Lokomat® settings; degree of active affected-leg movement in standing; physiological gait pattern and assistance required in a BWSTT trial.

In all three Lokomat® APF activities, a moderate intensity of CV exercise was achieved, demonstrated objectively by a mean (SD) VO_2 of 8.0 (3.8) ml/kg/min (estimated to 52% VO_2max), and a mean (SD) MET of 3.1 (1.3). This was supported by mean BORG scores between 3 and 5. VO_2 and MET were not affected by which APF activity was completed (p=0.110 and 0.240), with VO_2, MET and BORG results maintained over 15 minutes. Lokomat® body-weight support (BWS)

and guidance force (GF) significantly progressed (p<0.05) between study sessions as per clinical practice without significant changes in VO_2 or MET over the six study sessions (p=0.380 and 0.527). Motivation scores were consistent for all APF activities and within and between all study sessions, however enjoyment was greater for the Graph APF activity (p<0.001).

Comparison between the four participants clinically judged as ready for BWSTT and the six participants clinically judged not-ready for BWSTT revealed that BWSTT ready participants had: a) a FAC of 1; b) independence in sit to stand and standing balance with even weight-bearing; c) Lokomat® settings of BWS <30%, GF <30-35%, and speed >2.0kph; d) more than 45 degrees of standing active hip and knee flexion; e) no significant issues with their physiological stepping pattern in BWSTT that could not otherwise be managed with verbal or physical facilitation from only one person. An algorithm and proposed clinical decision-making tool were developed guiding the flow of assessment, using these factors, and aligned with concepts identified in previous literature of severity, assessment of assistance required, and assessment of volitional control.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

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1. LITERATURE REVIEW

1.1 Introduction

According to the Australian Institute of Health and Welfare (AIHW), there were more than 33,300 hospitalisations for stroke and 25,800 hospitalisations for rehabilitation following stroke in 2009-10 in Australia (AIHW, 2013). In 2016 alone, over 9000 cases were registered for inpatient rehabilitation with the Australasian Rehabilitation Outcome Centre (AROC), with between 20 to 30 per cent of these cases classified as more severely disabled with regard to functional ambulation (AROC, 2017). Limited ambulation is associated with an inability to return home (Tucak, Scott, Kirkman, & Singer, 2010), poorer quality of life (Franceschini et al., 2009), less participation (Danielsson, Willen, & Sunnerhagen, 2011; O'Sullivan & Chard, 2010), and greater levels of depression (Brown, Hasson, Thyselius, & Almborg, 2012). Regaining functional ambulation for the more severely disabled mobility-dependent patient post-stroke therefore remains as one of the key goals and challenges of subacute rehabilitation.

Meaningful functional ambulation, and the goal for rehabilitation relating to this, is to achieve what is known as community ambulation. This is defined, in part, by an ability to ambulate both indoors and outdoors (Lord, McPherson, McNaughton, Rochester, & Weatherall, 2004), and hence by definition necessitates a certain level of independence, as well as endurance, and therefore CV fitness. Having adequate endurance for community ambulation was an important factor identified by participants post-stroke in a recent study by Barclay, Ripat and Mayo (2015). Given that the hemi-paretic gait is more energy demanding than normal walking (Delussu et al., 2014; Ivey, Macko, Ryan, & Hafer-Macko, 2005), a more efficient quality of gait, and optimal CV fitness, are both important components of achieving successful community ambulation. A loss of independence is known to be related to CV fitness levels where VO_2max is below 18ml/kg/min (Shephard, 2009). Research has demonstrated that most people post-stroke fail to achieve this level when tested with peak oxygen consumption measures (Marsden, Dunn, Callister, Levi, & Spratt, 2013). Similarly, the energy demands to complete activities of daily living (ADL) as compared to the capacity available to the person post-stroke is discussed by many as an issue (Ivey et al., 2005; Michael, Allen, & Macko, 2005; Yates et al., 2004). It therefore appears that the research suggests that without adequate CV fitness post-stroke, the energy demands of walking or moving to complete daily tasks may be too great for participation in activities including personal care, desired daily tasks, or accessing the community.

1.2 Definition, Measurement and Recommendation for Cardiovascular Exercise in Subacute Stroke

Definition and prescription of exercise for people with stroke within current literature lacks detail regarding the specific key required criteria of Frequency, Intensity, Type and Time, known as the FITT principles (Ammann, Knols, Baschung, de Bie, & de Bruin, 2014). To meet criteria for CV 'type' of exercise, large muscle groups must be used in a repetitive fashion for a sustained minimum duration (time criteria) of 10 minutes, whereby three 10 minute blocks per day can accumulate to the 30 minute minimum time recommendation (American College of Sports Medicine, 2014). A frequency of three, to most days of the week, is also recommended for people post-stroke, in order to meet exercise and national guidelines (American College of Sports Medicine, 2014; Billinger et al., 2014; Stroke Foundation, 2017). Whilst the principles of frequency, time, and type are easy to measure, the measurement of intensity of CV exercise is more complex.

Concerns have previously been noted regarding consistency of methodology of exercise intensity testing in stroke, including: reporting and instructions used; device/modality used; termination criteria; and pathophysiology of the condition itself with regard to metabolic measures reviewed (Smith, Saunders, & Mead, 2012; Stoller, de Bruin, Knols, & Hunt, 2012; van de Port, Kwakkel, & Wittink, 2015; Wittink et al., 2017). Despite this, the gold standard for measuring CV fitness continues to be oxygen consumption analysis, known as VO_2 testing, completed via Cardio-Pulmonary Exercise Testing (CPET) for measurement of maximal aerobic capacity (Smith et al., 2012; Stoller et al., 2012; van de Port et al., 2015; Wittink et al., 2017). Recent advances in technology have seen the implementation of portable units for VO_2 testing, which have been shown to be feasible and reliable in the stroke population, both as a maximal and submaximal test (Eng, Dawson, & Chu, 2004; Stookey et al., 2013). Oxygen consumption reflects an individual's cardiorespiratory fitness through combined functionality of multiple body systems, including the cardiac, pulmonary, and musculoskeletal systems. As such, a VO_2 measurement can be affected by physiological changes in any of these systems, as well as by other factors including age, gender, and previous fitness training.

Related to oxygen consumption, MET is a measure of the energy cost of a specific activity, relative to rest. One MET, considered as rest, can be approximated as an oxygen consumption of 3.5ml/kg/min (Fletcher et al., 2013). However, the more accurate process to calculate the number of MET's for a particular individual completing a specific task is to compare the individual's mean VO_2 achieved while completing a task, relative to their measured mean resting VO_2 (Norton, 2010).

With the need for specialised equipment, the use of oxygen consumption analysis in clinical practice is not always feasible. A simpler option, using subjective self-assessment of CV exercise intensity, is provided by the BORG RPE scale. The original (6-20 point) RPE scale was developed to assess how hard a participant perceives they are working, with each number correlating reasonably well to a specified heart rate (HR) (Borg, 1982). The original scale has since been modified to include descriptors and a score from 0 to 10. This modified scale, known as the CR-10 scale, is often considered preferential to the original (Borg & Kaijser, 2006; Pageaux, 2016). A score of 11 to 13 on the original scale and 3 to 4 on the CR-10 scale is considered to represent moderate intensity CV exercise (Billinger et al., 2014; Zamunér et al., 2011). Sage et al. (2013) demonstrated validity of the CR-10 scale to VO_2 at moderate intensity exercise levels in patients with subacute stroke. Pageaux (2016) detailed the need for specified targeted questioning when using the BORG scale, and indicated that whilst the original intent was to assess overall perception of total body work, the scale could be used to target specific questions such as perceived effort of leg work (BORG-Leg (BORG-L)) versus breathing (BORG-Dyspnoea (BORG-D)). Using the CR-10 scale in healthy participants, Zamunér and colleagues (2011) found that responses given separately to both leg and respiratory RPE both correlated well to the anaerobic threshold at a score of 5. This outcome further supports a score of 3 to 4 on the BORG CR-10 scale as representative of moderate intensity, as well as the potential to use specific questions such as leg versus respiratory perceived effort.

HR provides another option for measuring CV exercise intensity (Billinger et al., 2014). However, HR may not be the most reliable measure given that it is influenced by many other factors such as medications, stimulants (coffee, nicotine), stress, anxiety, psychological factors, and visual stimulus (Smith et al., 2012). As such, VO_2 is generally considered as the more reliable measure. In support of this, Eng et al. (2004) found no correlation between HR and VO_2 in their research investigating relationships between submaximal and maximal treadmill, cycling, and walking tests in chronic stroke. Furthermore, Krewer et al. (2007) discussed that based on previous literature HR and VO_2 may not have a linear relationship in patients with CV disease, such that HR was not reviewed in their study. Stookey et al. (2013) concluded a need for further investigation into the use of HR, after reporting non-optimal correlation in test-retest HR measures when using a portable metabolic device (COSMED K4b2®) in overground walking in chronic stroke. A study on the Gait Trainer (GT) robotic in stroke also found HR and VO_2 did not correlate, with no statistical difference found for HR between test conditions of floor walking versus the GT robotic, whilst comparatively, a statistical difference was evident for VO_2 for the same test conditions (David et al., 2006).

CV exercise intensity is defined into low, moderate and high intensity as follows (American College of Sports Medicine, 2014; Norton, 2010; Riebe et al., 2015; Wittink et al., 2017):

- low = 30%-40% VO_2 reserve/2-3 MET/ 9-11 RPE original (CR-10 1-2);
- moderate = 40%-60% VO_2 reserve/3-6 MET/12-13 RPE original (CR-10 3-4);
- high = >/= 60% VO_2 reserve/6+ MET/14+ RPE original (CR-10 5+).

In the subacute stroke population, Billinger and colleagues (2014) recommend 20 minutes of moderate intensity exercise most days of the week, which is in line with the Australian national guidelines of 30 minutes of moderate intensity exercise most days while in subacute rehabilitation (Stroke Foundation, 2017). Whilst positive outcomes can be gained from lower intensity exercise, especially in the sedentary population (Fletcher et al., 2013), higher intensities are known to induce greater improvements in CV fitness (Billinger, Boyne, Coughenour, Dunning, & Mattlage, 2015).

1.3 Cardiovascular Fitness Levels Post-Stroke

Regardless of how it is measured, decreased CV fitness is known to be an independent risk factor for stroke (Gordon et al., 2004; Lee, Folsom, & Blair, 2003; O'Donnell et al., 2010) and CV disease (Myers et al., 2015). An individual's pre-morbid CV fitness may therefore negatively influence post-stroke CV fitness (Billinger, Coughenour, Mackay-Lyons, & Ivey, 2012a; Smith et al., 2012). This concept is supported by Baert and colleagues (2012), who found that patients with stroke were more at risk of deterioration in their CV fitness post-stroke if they were less active prior to their stroke. Besides pre-existing activity levels, poor post-stroke CV fitness is considered multi-factorial, relating to the multi-organ physiological changes and interplay of the cardiac, vascular, pulmonary and musculoskeletal systems, which may be affected directly from the neurological damage itself, or the resultant imposed immobility (Billinger et al., 2012a; Ivey et al., 2005).

Despite the recognised potential in stroke for pre-existing low CV fitness, subacute patients post-stroke have been shown to have around half the CV fitness capacity of age and gender matched, sedentary but healthy individuals within two weeks to six months post-stroke (Chen, Chen, Chen, & Huang, 2010; Duncan et al., 2003; Gordon et al., 2004; Kelly, Kilbreath, Davis, Zeman, & Raymond, 2003; Mackay-Lyons & Makrides, 2002; Tang, Sibley, Thomas, McIlroy, & Brooks, 2006; Yates et al., 2004). In their systematic review, Smith and colleagues (2012) found an average of 53% peak aerobic capacity following subacute and chronic stroke in comparison to healthy sedentary individuals, with a range of peak oxygen consumption of between 8 and 22 ml/kg/min. Marsden et al. (2013), in their review on both subacute and chronic stroke, found 24 out

of 28 included studies had patients post-stroke falling below the 18ml/kg/min VO_2 level needed for independence.

In a longitudinal study of CV fitness following stroke, Baert and colleagues (2012) found no change in the CV fitness levels of their participants over a 12 month period. This indicates that the reduced CV fitness, which can occur as early as two weeks post-stroke, is typically sustained long term. This is consistent with several studies in chronic stroke demonstrating CV fitness levels of around 50% compared to age and gender matched sedentary populations, which is similar to that found in the subacute stage (Eng et al., 2004; Ivey et al., 2005; MacKay-Lyons & Makrides, 2004; Michael et al., 2005; Pang, Eng, Dawson, & Gylfadóttir, 2006). The longitudinal study by Baert et al. (2012) is supported by a systematic review demonstrating ongoing chronically low CV fitness, matched with low levels of activity and high sedentary behaviour in patients with stroke living in the community (English, Manns, Tucak, & Bernhardt, 2014). The exact reasons for such low levels of active participation are multi-factorial, however Baert et al. (2012) found those at the highest risk of a deteriorating CV fitness were those who were less active prior to their stroke, diabetic, and more severely affected. This low level of post-stroke CV fitness does not just imply a restriction on participation in activities, but also relates poorly to secondary prevention measures, which are important given the known high percentage of recurrent stroke (Smith et al., 2012).

1.4 Cardiovascular Exercise for Improving Cardiovascular Fitness in Subacute Stroke

CV exercise is considered effective and important in improving the low levels of post-stroke CV fitness (Brazzelli, Saunders, Greig, & Mead, 2011; Pang, Charlesworth, Lau, & Chung, 2013; Pang et al., 2006; Saunders, Greig, & Mead, 2014), including in the sub-acute stroke population (Duncan et al., 2003; Sandberg, Kleist, Falk, & Enthoven, 2016; Stoller et al., 2012; Tang et al., 2009). MacKay-Lyons and Makrides (2004) proposed that there is a degree of “spontaneous” recovery in CV fitness in the first two months post-stroke due to pathophysiological recovery and participation in general daily tasks that were not specifically targeted as CV training. It should be noted however that all participants in this study by MacKay-Lyons and Makrides (2004) were participating in a rehabilitation program. Whilst this rehabilitation program was known to not elicit an intensity to be classified as CV training, training of low intensity is known to have an impact on CV fitness (Fletcher et al., 2013), which may explain the results labelled as spontaneous recovery by MacKay-Lyons and Makrides (2004). Using a control group where no rehabilitation intervention was completed, Sandberg et al. (2016) reported no spontaneous recovery, highlighting the importance of using a specific CV exercise intervention to create physiological adaptation. The effects of targeted and specific CV exercise in patients with stroke are known to be widespread, across multiple physiological systems (Billinger et al., 2012a), with even a small increase in CV

fitness considered beneficial from the perspective of increasing independence with ADLs (Ivey, Hafer-Macko, & Macko, 2006).

The subacute phase is known to be a particularly challenging time to adequately provide CV exercise to mobility-dependent patients with stroke, with more limited options existing regarding modality of exercise due to immobility (Billinger et al., 2014; Lefeber et al., 2016; Stoller et al., 2015; Tang et al., 2009). As this group are at the most risk of a deteriorating CV fitness level in the first 12 months post-stroke (Baert et al., 2012), it is important to develop effective strategies to address this. Evidence has demonstrated that conventional physiotherapy often provides only a small amount of active dosage, with patients often resting or sitting for a large percentage of their therapy session (Kaur, English, & Hillier, 2012; Mackay-Lyons & Makrides, 2002; Prajapati, Gage, Brooks, Black, & McIlroy, 2011). As such, conventional therapy offers little in the way of CV exercise (Kuys, Brauer, & Ada, 2006; Mackay-Lyons et al., 2013). For example, a recent study on inpatients with stroke in rehabilitation found over 80% of walking bouts were less than one minute, with no participant in the study meeting the dosage requirements of time or intensity needed for a CV training effect (Prajapati et al., 2013). The lack of effective CV exercise dosage in therapy appears to be consistent with the findings in the longitudinal study by Baert et al. (2012), which reviewed patients at three, six and 12 months post stroke. The findings of this study included that there was no significant change in CV fitness at any stage over the 12 months, including during the subacute stage while in rehabilitation and completing therapy (Baert et al., 2012).

Several factors have been considered as to why CV exercise may not be incorporated into standard rehabilitative care, including: staffing capacity, confidence or resources; availability of effective treatment options; and an emphasis on other activities (Marsden et al., 2013). Research shows, however, that there are effective modalities that can be safely implemented to elicit a change of CV fitness related parameters in patients with stroke, including in the subacute phase (Chang, Kim, Huh, Lee, & Kim, 2012; Duncan et al., 2003; Letombe et al., 2010; Stoller et al., 2012; Tang et al., 2009). A meta-analysis covering subacute and chronic stroke found a 10-15% increase in VO_2 peak from specifically provided CV training (Marsden et al., 2013), which is consistent with results of another meta-analysis (Pang et al., 2013). Collectively, these reviews of the literature demonstrate the effectiveness of modalities for CV fitness training in stroke when the modality is specifically included in intervention as a part of research.

1.5 Methods of Achieving Cardiovascular Exercise in Subacute Stroke

Many forms of CV exercise can be used in the stroke population, such as supported treadmill walking, seated cycling, water-based exercise, recumbent steppers, and home-based exercise programs (Billinger et al., 2015; Ivey et al., 2006). For example, two studies (Billinger et al., 2012b; Mattlage, Ashenden, Lentz, Rippee, & Billinger, 2013) used recumbent steppers three times per week for eight weeks in the subacute (less than six months) stroke population to demonstrate improvements in measures relating to CV fitness. Functional task specificity and the benefits of walking-based CV fitness activities have however, previously been recognised as important, wherein fitness-based benefits of other activities did not translate into the same improvements in walking fitness or functional outcomes for gait (Brazzelli et al., 2011; Gordon et al., 2004; Jin, Jiang, Wei, Wang, & Ma, 2012; Kelly et al., 2003). This is noted in a study by Jin et al. (2012), where gains made in CV fitness from cycling did not greatly influence walking ability. Brazzelli et al. (2011) further state in their systematic review of physical fitness in stroke, that walking training may be beneficial in providing a more task specific activity, accomplishing both an increase in CV fitness and change in gait efficiency through improvements in gait speed and capacity. Kelly et al. (2003) suggest that treadmill training may elicit greater CV workloads than bicycle ergometry, however, more caution is needed in who can safely participate in this option, with some patients benefiting from a body-weight supporting harness. Evidence exists that BWSTT in stroke provides effective outcomes for CV fitness when compared to conventional therapy (Mackay-Lyons et al., 2013), such that BWSTT is a feasible modality choice for patients that can complete this activity. For the more dependent patient post-stroke, it is acknowledged that walking-based activity for CV fitness may not be feasible, at least not without the relatively new advance in technology of robotic assisted treadmill walking (Stoller et al., 2015).

1.6 Robotic Assisted Treadmill Walking and Cardiovascular Exercise

A recent systematic review indicates that in general, robotic assisted walking, especially where some BWS is provided, is likely to be less CV taxing than treadmill or overground walking (Lefeber et al., 2016). Variables such as the device type, device settings used, active participation from the participant, and type and severity of impairment, are all acknowledged as potentially contributing to CV workload outcomes (Lefeber et al., 2016). Because of this, the authors acknowledged a large degree of heterogeneity with regards to devices used, patient population (a mix of disabled and healthy participants), test variables (overground, treadmill, and robotics), as well as device settings represented within their systematic review. Only one study in patients with stroke using the Lokomat® was included (van Nunen, Gerrits, de Haan, & Janssen, 2012), and only two other studies in patients with stroke using a similar device - the GT robotic (David et al., 2006; Delussu et al., 2014).

The study by van Nunen and colleagues (2012) compared six minutes of overground walking to an unspecified time of Lokomat® use in 10 participants who were 10 to 79 weeks post-stroke. Stroke participants, during Lokomat® training, were reported in this study as not reaching the minimum 30% HR reserve (HRR), defined as low intensity exercise. However, the specific data on stroke participants is not included for review, presented data includes comparison to healthy non-stroke participants, no information is given regarding device settings for GF, BWS, or speed for stroke participants, and no detail is provided of any training activity or motivation and feedback used while on the Lokomat®. Furthermore, whilst the included stroke participants were reported as not able to reach 30% HRR on the Lokomat®, caution is again required in considering HR as reliable or valid in this population. Data presented on MET's in this study, using VO_2 to calculate the MET, was more promising for participants having attained a moderate intensity level of CV exercise, a concept supported by Han, Im, Kim, Seo, and Kim (2016). Again, however, the detail of VO_2 or MET values were not presented in enough detail to ascertain the intensity levels achieved for participants with stroke on the Lokomat®. Regardless of the intensity of CV exercise achieved, the participants in the study by van Nunen and colleagues (2012) were able to attempt to complete a six-minute walk test overground, and therefore are not representative of the more disabled non-ambulatory patients for whom overground walking for CV exercise is not possible.

In their 2006 study using the GT robotic in subacute stroke, David and colleagues (2006) found overground walking to result in higher VO_2 measures than were found with use of the GT robotic. This study did not report the intensity of exercise achieved, and only one participant with stroke could sustain the six-minute walking duration overground, which is not enough duration to meet the time criteria for CV exercise. The need to provide a longer duration of walking-based CV training than can be provided to patients with stroke overground is also mentioned by Han et al. (2016) and van Nunen et al. (2012). Furthermore, the participants included in the study by David et al. (2006) were again not representative of the more disabled, non-ambulatory patients for whom provision of CV exercise is challenging, or impossible, with overground options. In another study on the GT robotic, Delussu et al. (2014) compared overground walking to the GT in subacute stroke patients and also found overground walking yielded higher VO_2 results, as did lower levels of BWS on the GT. The exception to a higher demand from overground walking was found when no BWS was provided on the GT, wherein a greater VO_2 workload than overground training was demonstrated with the GT. This is in contrast to the study by David et al. (2006) on the same device with a similar group of patients, where no difference was found in VO_2 outcomes with a change of BWS. Again, Delussu et al. (2014) made no mention in the study as to what intensity of CV exercise participants reached. As discussed by Lefeber et al. (2016) and Morone et al. (2017), the results of research into CV exercise on robotics may be device and setting specific, relating to the different robotic

deign, warranting further review of the Lokomat® device and any other studies specific to the Lokomat® not included in the systematic review.

1.7 The Lokomat® Robotic

The Lokomat® robotic walking device has been demonstrated as an effective tool in the rehabilitation towards ambulation of the more dependent patient with stroke (Mehrholz, Elsner, Werner, Kugler, & Pohl, 2013; Mehrholz et al., 2017b; Morone et al., 2012; van Nunen, Gerrits, Konijnenbelt, Janssen, & de Haan, 2015). This is without compromise to outcomes of walking speed or endurance (Ada, Dean, Vargas, & Ennis, 2010b), or muscle activation patterns (Coenen et al., 2012; Gizzi et al., 2012). The device has been described in detail elsewhere (Riener, Lünenburger, Maier, Colombo, & Dietz, 2010). In brief, it provides body-weight supported treadmill walking with the use of a robotic orthosis to assist the movement of the lower limbs, whilst still allowing the patient to participate actively in walking. Given the supported upright walking motion, the use of the device is considered clinically to provide a potential option for CV exercise, particularly for mobility-dependent patients post-stroke. Several parameters of the Lokomat® can be changed to challenge the patient, including BWS, GF, and speed of overall movement. Recent studies have demonstrated that higher CV workloads can be achieved by lowering the BWS and GF, and increasing speed (Lefeber et al., 2016; Schindelholz, Stoller, & Hunt, 2014; Stoller et al., 2013; van Nunen et al., 2012). A single-subject crossover design study (Krishnan, Kotsapouikis, Dhaher, & Rymer, 2013a) further supported using a lower GF to positively affect mobility related functional outcomes. Another study suggests lower BWS and higher speeds normalise temporal patterns and muscle activity when comparing robotic walking to unaided treadmill walking (Van Kammen, Boonstra, Reinders-Messelink, & den Otter, 2014).

Sensors, located within the hip and knee articulations of the orthosis, respond to patient activity, with the level of effort provided by the patient integrated into the APF activities of the Lokomat®. The patient activity and APF activities are displayed on a screen, creating a virtual reality biofeedback environment to encourage, and monitor, active patient participation through “reward” based game incentives, or real-time quantitative graph feedback. A range of different APF activities are available including “Faster”, “Graph” and “Gabarello 2” in the version 6 software. These three APF activities are suitable for use within a wide range of the GF setting and have a low cognitive challenge, making them common clinical choices in subacute rehabilitation.

1.8 The Lokomat® Robotic and Cardiovascular Exercise

Most research relating to the Lokomat® and CV exercise has so far either focused on the use of the Lokomat® for CPET (Stoller et al., 2014a; Stoller et al., 2013; Stoller et al., 2014b), or a change of CV fitness pre and post a Lokomat® training phase (Chang et al., 2012; Stoller et al., 2015). In a series of work by Stoller and a range of colleagues (Stoller et al., 2014a; Stoller et al., 2013; Stoller et al., 2014b), the feasibility, reliability, and repeatability of using the Lokomat® robotic for evaluation of CV exercise capacity was established. The focus of this series of work was to ascertain if the Lokomat® robotic could be used as an alternative to bicycle ergometry or treadmill exercise testing for completion of CPET in the more dependent patient early (acute to subacute) after stroke. In order to test this, Stoller and colleagues (2013, 2014a, 2014b) developed their own feedback mechanism described as Feedback Controlled Robotic Assisted Treadmill Exercise (FC-RATE). In this system, participants received visual information relating to their target and actual workload according to mechanical work within the Lokomat®. This system was designed to encourage a maximal work rate to a target HR, guided by visual feedback of the mechanical work generated via leg effort sensed by the device orthosis. Whilst the feasibility, reliability, and repeatability were established, concerns were raised as to whether participants were meeting the recommended intensity of exercise. This was due to only 57% of participants meeting one of three criteria for a maximal CPET, and all participants stopping due to either generalised or leg fatigue (Stoller et al., 2014a; Stoller et al., 2013; Stoller et al., 2014b).

Whilst current literature suggests it is difficult for the mobility-dependent subacute patient with stroke to achieve more than a low intensity of CV exercise on robotic devices, it is known that people who are more deconditioned may still benefit from lower levels of CV exercise intensity (Fletcher et al., 2013). This is supported by two studies who found an improvement in CV fitness levels, two and four weeks post a Lokomat® training phase (Chang et al., 2012; Stoller et al., 2015). Chang and colleagues (2012) compared a two week training program of equal dosage of conventional therapy (100 minutes) to a combination of conventional and Lokomat® therapy (60+40 minutes) in subacute (<1 month), mobility-dependent (FAC <2), patients with stroke. Results indicated that the group receiving Lokomat® therapy had a 12.8% greater improvement in peak VO_2 compared to the conventional therapy group. In this study, intensity is only described as being controlled by the therapist, with both therapist and patient monitoring treadmill speed, joint speed, and joint angle, highlighting the issues noted by Ammann et al. (2014) regarding details of exercise using the FITT principles not commonly being included in stroke literature. No details of any activities completed whilst on the Lokomat®, or the participant's actual training intensity achieved, are included.

In 2015, Stoller and colleagues compared their self-designed FC-RATE therapy (described above) to an equivalent dosage of conventional Lokomat® therapy over four weeks in mobility-dependent (FAC 0-2) subacute patients with stroke. In this research, participants using the FC-RATE feedback mechanism had a higher training intensity according to the percentage of HRR achieved, but both groups improved their CV fitness without statistical significance between groups. There was, however, no description of any activities, motivation, or feedback given during conventional Lokomat® therapy, such that other forms of feedback may also be effective in increasing higher training intensities. Despite the higher percentage of HRR achieved with FC-RATE, optimal training intensities for moderate intensity CV exercise were considered by the authors to have only been met by 42% of the group completing the FC-RATE based training. This outcome further highlights the challenges of achieving moderate intensity CV exercise for mobility-dependent patients with stroke on the Lokomat®.

1.9 Feedback Options for Increasing Cardiovascular Workload and Patient Activity in Robotics

Whilst it has been demonstrated that patients are never entirely passive while walking in the Lokomat® robotic (Krewer et al., 2007; Stoller et al., 2013), the question remains as to whether patients can be active enough to meet exercise guidelines by achieving optimal levels of moderate intensity CV exercise, sustained for a minimum duration of 10 minutes. A study by Koenig et al. (2011) assessed if patient participation could be controlled via voluntary effort, speed, or feedback about performance using HR or a virtual reality feedback activity. Along with the alternatives of increased speed, lower BWS, and lower GF to drive higher patient workload, this study also reviewed the use of the weighted sum of interaction torques (WIT). This relates to the torques that patients produce by resisting, working with, or pushing against the Lokomat® orthosis, and is similar to the Graphs APF activity. The study also used virtual reality based feedback, similar to other APF activities of the Lokomat®, which the authors suggest may assist in enhancing CV training (Koenig et al., 2011). This study, whilst looking to quantify patient activity by HR and torque forces through either voluntary effort with visual interaction or via an increase in treadmill speed, did not review if the actual workloads achieved constitute moderate intensity CV exercise. What was determined is that CV workload can be controlled via speed or voluntary effort to achieve a target HR, or via attempts to achieve the desired outcome on the virtual reality task. Furthermore, the study concluded that individual patient characteristics, such as cognition and limb ability, may play a role in determining which method is best used to achieve a desired training target.

Whilst the study by Koenig et al. (2011) investigated the potential use of a HR controlled workload on the Lokomat®, the authors also acknowledge the limitations of HR use due to factors such as

beta-blockers, and stimulants like caffeine or nicotine. The authors also state the challenges of extra equipment (an ECG monitor was used) to assess HR, suggesting that clinically the RPE BORG scale may be more appropriate. Recently, Bae, Kim, and Fong (2016) compared use of HRR and RPE on the Lokomat® in chronic stroke patients. Their conclusion was that use of HRR as the target for training improved particular motor outcomes over training with the RPE target. However, whilst a target of 70% HRR and 15 RPE was set, no detail was given regarding whether the groups actually achieved these targets, how feedback was given to participants for reaching the targets, or how the intensity of training was adjusted via mechanisms such as speed, GF, or BWS. As such, there may have been differences between the groups that could have also influenced outcomes. Furthermore, no indication of use of virtual reality or specific feedback mechanisms were given, which are supported by both Koenig et al. (2011) and Stoller et al. (2015) as enhancing achievable CV workloads. Whilst in the study by Stoller and colleagues (2015), HR was also used, and every participant reached one of three criteria to ensure the CPET was a maximal exercise test (plateau in VO_2, RER peak, or HR peak), participants ultimately stopped due to either generalised fatigue or leg fatigue. Fatigue is a subjective measure relating more to an individual's perception, and can be assessed using the RPE BORG scale. Assessing whether the participant's perceived workload, both in terms of dyspnoea and leg effort is similar to actual VO_2 achieved, for subacute patients with stroke whilst active on the Lokomat®, would therefore seem important.

In the study by Bae et al. (2016), the fact that participant's motor function improved when aiming for a higher CV workload supports that participants in that study were using their affected leg actively. This is a concept that has previously been suggested by Stoller et al. (2015) to be a potential issue. The use of the WIT based concept, in combination with virtual feedback as per Koenig et al. (2011), also diminishes the issue of possible non-use of the affected leg. This concept is incorporated into the Lokomat® robotic system via the APF activities. When using their own muscle activity to attempt to move the limb, the APF activities are designed to reward patients within the virtual reality environment presented on the patient screen. Clinically, the APF activities of the Lokomat® are more commonly used to enhance motivation, engagement, and enjoyment, as well as provide feedback on lower limb use and activity. Several APF activities exist within the Lokomat® software, and certain activities may elicit a higher CV exercise intensity than others. As Hocoma regularly change and update their APF activities, investigation into the influence of a variety of APF activities is important and may guide future software development. With concerns that participants may be predominantly using their unaffected side in achieving potential CV training (Stoller et al., 2015), and the evidence that WIT and virtual reality feedback may enhance CV workload (Koenig et al., 2011), the use of the APF activities may be more beneficial in not just ensuring, monitoring, and providing feedback of use of the affected side, but also in enhancing CV

workload. This concept is supported by a study demonstrating the use of a foot tracking task to improve muscle activation, and hence active participation, while walking in the Lokomat® (Krishnan, Ranganathan, Dhaher, & Rymer, 2013b), adding further evidence of the need to investigate the influence of the different APF activities on CV workload.

1.10 Body-weight Supported Treadmill Training as an Alternative to Robotic Assisted Locomotor Therapy

BWSTT has previously demonstrated advantageous outcomes as a functional walking task-specific therapy option for CV exercise in subacute stroke (Mackay-Lyons et al., 2013). BWSTT consists of a form of patient harness suspended over a treadmill to reduce the weight bearing forces of the patient's own body weight through their lower limbs, therefore lessening the work and challenge required to stand upright against gravity on a weakened leg in stance, as well as allowing safety and balance for swing (Backus & Tefertiller, 2008; Crompton et al., 2001; Hesse, 2008; Hornby, Zemon, & Campbell, 2005). Stand-alone devices such as a suspension frame or gantry with walking sling and standard treadmill can be used for this purpose, or the Lokomat® can be used once the robotic orthosis is removed from the patient's limbs. Regardless of the specific equipment used, in BWSTT the trunk and body weight remain partially supported, but the lower limbs are free of any specific assistive device, thereby increasing the requirement, as compared to mechanically assisted robotics, for the patient to move the lower limbs more actively and independently (Backus & Tefertiller, 2008). Concurrently, the patient has to work to a greater degree with no mechanical assistance on stance, balance, timing, and symmetry of movement, while still receiving some degree of trunk and balance support via the harness (Backus & Tefertiller, 2008). BWSTT was originally introduced in spinal cord injury (SCI) rehabilitation in the mid-1980s and may be provided with or without additional manual therapist assistance to move one or both legs or support the trunk or pelvis (Barbeau, Wainberg, & Finch, 1987). Where additional support of this nature is provided, BWSTT is commonly described as manual or therapist assisted BWSTT, with anything from one to three therapists providing support.

1.11 Advantages and Disadvantages of Robotic and Body-weight Supported Treadmill Training Modalities of Locomotor Therapy

The time and costs incurred by BWSTT using multiple therapists providing potentially physically taxing manual assistance prompted the introduction of robotic devices to minimise both the number of therapists required, as well as the physical demand on therapists (Hesse, 2008; Hornby, Reinkensmeyer, & Chen, 2010; Manickavasagam, Paranthaman, Alagesan, & Rathod, 2015; Mehrholz et al., 2017b). The number of therapists required, and physical demands placed on, therapists during BWSTT are noted as potential advantages of robotic therapy over both BWSTT

or overground locomotor training, along with more symmetrical repetitive stepping of greater duration and dosage that can also be completed more safely (Backus & Tefertiller, 2008; Backus, Winchester, & Tefertiller, 2010; Hornby et al., 2010; Manickavasagam et al., 2015). Additionally, when compared specifically to BWSTT, advantages of robotic therapy include: the ability to more precisely set, adjust and monitor the amount of assistance and joint range of motion provided; the virtual reality environment capable of receiving, displaying and incorporating biofeedback; and the ability to measure patient ability quantitatively (Backus & Tefertiller, 2008; Backus et al., 2010; Hornby et al., 2010; Manickavasagam et al., 2015). Potential disadvantages or concerns regarding robotic therapy include: fixed ranges of motion without kinematic variability for learning; passive dorsiflexion; upper speed limits of the device; and perhaps of greatest concern, the potential for passive over-support, risking no active participation by patients and thereby defeating the purpose of therapy (Backus & Tefertiller, 2008; Hornby et al., 2005; Manickavasagam et al., 2015).

The inherent need for patients to be more active, leading to a higher CV workload in BWSTT is one advantage of this modality over robotic therapy. Other advantages include the potential for more controlled and specific sensory input, the ability to make minor therapist adjustments to the assistance provided per step, and the opportunity to learn through error via variability in stepping practice (Backus & Tefertiller, 2008; Manickavasagam et al., 2015). Compared to overground training, particularly in more severely affected mobility-dependent stroke patients, BWSTT provides the potential for a greater duration and dosage of task-specific repetitive stepping practice, provided in a safe way, with no risk of falls, less therapist strain, and added trunk and balance support (Ada, Dean, Morris, Simpson, & Katrak, 2010a; Backus & Tefertiller, 2008; Crompton et al., 2001; Hornby et al., 2010). Disadvantages and concerns regarding the amount of therapist assistance not being quantified, inability to monitor patient effort accurately, difficulty of task completion with spasticity, and the potential need for an increased number and effort of therapists also exist for BWSTT (Backus & Tefertiller, 2008).

1.12 Efficacy of Locomotor Training Modality

With advantages and disadvantages to both robotic and BWSTT therapy, the choice of which modality to use throughout varying stages of a patient's rehabilitation journey, or whether to complete conventional and overground training instead, continues to be difficult (Backus & Tefertiller, 2008; Hornby et al., 2010; Hornby et al., 2005). The literature reviewing the functional benefits of the different modalities of locomotor training in stroke is also conflicting (Backus & Tefertiller, 2008; Hornby et al., 2010; Mao et al., 2015; Westlake & Patten, 2009), with heterogeneity of methodological quality, patient populations, and outcome measures used, as well as different combinations of comparisons of modalities hindering conclusions (Backus et al., 2010).

Other variables within the current research making comparisons difficult include: variance in intensity and dosage of therapy; differing amounts of manual therapist assistance provided or robotic device settings used; addition or exclusion of hand or upper limb use; a range of patient characteristics, including acute to subacute patients of differing stroke severity; and concomitant walking ability, ranging from ambulatory to non-ambulatory (Behrman et al., 2005; Hornby et al., 2011).

A recent Cochrane review in stroke found that robotic therapy, in conjunction with conventional therapy, is potentially preferable over other forms of therapy alone for mobility-dependent subacute patients with stroke with a FAC less than 4 (Mehrholz et al., 2017b). Additionally, outcomes from robotic therapy in ambulating patients with stroke were considered less efficacious (Mehrholz et al., 2017b). Duschau-Wicke, Caprez, and Riener (2010), Hornby et al. (2005) and Manickavasagam et al. (2015) reiterate that robotic outcomes seem to have been favourable for mobility-dependent patients when the need for assistance is high, while conventional therapy outcomes are more favourable for ambulating patients. However, consecutive Cochrane reviews on BWSTT in stroke conclude few beneficial outcomes overall, bringing into question the efficacy of utilising this modality at all (Mehrholz, Pohl, & Elsner, 2014; Mehrholz, Thomas, & Elsner, 2017a; Moseley, Stark, Cameron, & Pollock, 2005). The quality of early included studies on BWSTT is noted as questionable, and more recent studies have been described as being of low to moderate quality (Mehrholz et al., 2017a; Moseley et al., 2005). The more recent Cochrane review concluded that BWSTT may improve velocity and endurance in ambulatory patients with stroke however, improvements in overall ability to be independent were not supported (Mehrholz et al., 2017a). Nevertheless, community ambulation speed and endurance for community ambulation post-stroke have previously been noted as important and related to independence (Barclay et al., 2015). Overall, when considering the Cochrane reviews on both modalities it would appear that robotics may be preferable for non-ambulant and mobility-dependent patients (FAC <4) but less so for more mobile ambulant (FAC 4,5) patients, while BWSTT, if beneficial at all, may be more preferable for mobile patients with results less favourable and unclear for mobility-dependent and non-ambulatory stroke patients (Mehrholz et al., 2013; Mehrholz et al., 2014; Mehrholz et al., 2017a; Mehrholz et al., 2017b; Moseley et al., 2005).

Low quality evidence and inconclusive results noted in the 2005 Cochrane review (Moseley et al., 2005) regarding the use of BWSTT in mobility-dependent subacute patients with stroke led to a study on 126 subacute non-ambulatory patients with stroke comparing BWSTT to conventional overground therapy (Ada et al., 2010a). The results of this study were that, compared to overground therapy, BWSTT led to a greater incidence of an independent gait and earlier

discharge home (Ada et al., 2010a). Additionally, greater walking capacity was found in the same group of participants at six month follow-up (Dean et al., 2010). The results of these studies are supported by others (Barbeau & Visintin, 2003; Hornby et al., 2011; Mao et al., 2015; McCain et al., 2008) who demonstrated that BWSTT was potentially more beneficial than robotics, or overground training, across a range of different outcomes for non-ambulant patients with subacute stroke. Increased dosage of repeated stepping afforded by the safe and supportive use of BWSTT has been described as the main reason for improvements from BWSTT in non-ambulant subacute patients with stroke (Ada et al., 2010a). The suggestion that what is making a difference to outcomes is ultimately the dosage of repetitive movements, rather than the specific modality of locomotor training used, is supported by others (Behrman et al., 2005; Hornby et al., 2010). This support includes a study specifically designed to provide high dosage overground locomotor training using bracing and therapist support in mobility-dependent subacute stroke (Kosak & Reding, 2000). While the study by Kosak and Reding (2000) found that high dosage overground training was as beneficial as BWSTT, it was also acknowledged that the overground therapy could not be provided to the most dependent patients. In reality, it is also known that minimal steps and active dosage typically occur in conventional therapy (Kaur et al., 2012; Prajapati et al., 2013), particularly for mobility-dependent patients who cannot practice safely in this manner. As such, BWSTT of similar duration and stepping dosage is likely to provide more repetitive task practice than overground training, or at least be a useful therapy adjunct that may be considered equally as effective as other modalities (Franceschini et al., 2009).

With treadmill training known to have some differences in gait biomechanics compared to overground walking (Apte, Plooij, & Vallery, 2018), therapists have reported concern that without adequate motor control, patients completing BWSTT are at risk of repeatedly practicing, and hence potentially reinforcing, altered biomechanics with poor quality kinematic or spatiotemporal patterns (Hesse, 2008). In contrast, certain studies have noted preferential outcomes for BWSTT in these areas (Brouwer, Parvataneni, & Olney, 2009; Mao et al., 2015; McCain et al., 2008), with the suggestion that the improvements gained in kinematic and spatiotemporal parameters are due to repetitive practice with inherent step variability (Hornby et al., 2011; Manickavasagam et al., 2015). Therefore, an important advantage of BWSTT is the opportunity to learn from the errors in movement that can occur from both between-limb and within-limb variability in stepping that is only possible in BWSTT and overground training, but not with the more controlled robotic movements (Lewek et al., 2009; Manickavasagam et al., 2015). Although there is some degree of variability per step within the Lokomat® (Hidler, Wisman, & Neckel, 2008), the inherent variability of steps would still be greater in BWSTT (Backus & Tefertiller, 2008). The variability of steps within the Lokomat® can be enhanced with the use of a path control setting, potentially leading to better outcomes when used in robotic training (Duschau-Wicke et al., 2010). However, the path control setting can only be

used at lower GF settings which are not managed by all patients. Step variability potentially leading to greater clinical improvement from BWSTT, as compared to robotic therapy, may partly explain the improvements in the BWSTT group, as compared to the robotic group, for chronic stroke participants in the study by Hornby et al. (2008). However, in this study there was no mention of the robotic GF used, which would also influence outcomes (Hornby et al., 2008).

1.13 The Clinical Decision Regarding Modality Choice for Locomotor Therapy

While acknowledging the ongoing conflicting research results, there is some evidence that in subacute patients with stroke, BWSTT may provide benefit via safer access to higher dosage of repetitive task-specific stepping practice with greater spatiotemporal and kinematic variability and less risk of passive over-assistance. The potential for passive over-assistance from the robotic, a predetermined trajectory that does not allow variable limb kinematics, altered sensory input, and the limited maximal speed of the orthotic, are considered reasons for an early transition to BWSTT (Hornby et al., 2005). However, the clinical decision of when a patient is functionally ready to transition from robotic assisted gait training to BWSTT remains challenging (Backus & Tefertiller, 2008; Hornby et al., 2005) and is considered a “grey zone” (Duschau-Wicke et al., 2010; Hornby et al., 2010). Broadly, severity of impairment, amount of assistance required, and degree of volitional control in stepping are presented in the literature as three concepts to consider in the decision-making between the modalities of robotics and BWSTT (Backus & Tefertiller, 2008; Hornby et al., 2010; Hornby et al., 2005). Other than the recommendation in consecutive Cochrane reviews to trial robotics in patients with stroke with a FAC less than 4 (Mehrholz et al., 2013; Mehrholz et al., 2017b), no literature was found on specific criteria for modality choice or progression of therapy from robotics to BWSTT in stroke. Two articles were identified providing clinical decision-making algorithms for progression from the Lokomat® to BWSTT (Backus & Tefertiller, 2008), and progression of BWSTT training parameters (Behrman et al., 2005), in SCI. Manickavasagam et al. (2015) propose that the use of a clinical decision-making algorithm, similar to that developed for SCI by Backus and Tefertiller (2008) as described below, may be useful for other conditions such as stroke, and where the choice of both training modalities is available.

1.14 Existing Algorithms and Literature Regarding Modality Choice in Spinal Cord Injury

In the algorithm by Backus and Tefertiller (2008), the first item is assessment of motor “severity” using the American Spinal Injury Association (ASIA) classification of SCI. The outcome of the assessment is that more severely motor-affected patients all complete a trial on the Lokomat®. For patients with some initial motor ability, the second item is assessment of spasticity using the Spinal Cord Assessment Tool for Spasticity (SCATS), as well as assessment of trunk control and trunk strength using manual muscle testing and observation of sitting and standing trunk posture. The

authors consider the second item (assessment of spasticity, trunk control and trunk strength) to influence the amount of manual assistance required to complete a normal step, and hence the decision of whether or not to use the robotic. The third item in their algorithm is the assessment of overground or voluntary stepping ability, using the Functional Independence Measure (FIM) ambulation criteria of the level of assistance required to achieve 50ft (15-16m) as the cut-off between use of the robotic or BWSTT. Patients with SCI with some motor ability but increased spasticity, with manually tested weak trunk muscles, or poor observed sitting or standing trunk control, requiring more than one person to walk, or who are not able to walk more than 15-16 metres, are directed to the Lokomat®. However, patients with SCI with some motor ability, less spasticity, better manually tested trunk muscles with improved sitting and standing trunk control, who can walk overground 15-16 metres or more, with or without an aid, and with limited assistance from one person, are directed to BWSTT. It is suggested that an overall consensus of two out of three items determines the final decision. Moreover, readiness for transition from the robotic to BWSTT is recommended to be reassessed regularly by re-applying the algorithm, taking into account patient improvement.

Behrman et al. (2005) presented a single case study of a 55 year old SCI patient and the use of two clinical decision-making algorithms with regards to ability to complete BWSTT and progress BWSTT therapy training parameters. As a single case study results must be interpreted with caution, however static and dynamic components of standing posture and stepping ability form the basis of the decision-making algorithms presented by Behrman et al. (2005). Similar to Backus and Tefertiller's (2008) recommendation to reassess patients using the algorithm on a regular basis, Behrman et al. (2005) used the decision-making algorithm during each training session to inform changes to BWS and speed, or the addition or removal of verbal cueing or manual assistance. Standing posture included: review of the head being extended and midline; shoulders being back and symmetrical; trunk being upright and midline; hips being forward and symmetrical; knee straightness without being locked; and even weight distribution between both legs. Stepping ability was further broken down into: the ability to initiate stepping with good posture and balance; the ability to shift weight in standing and stride stance; the ability to initiate swing from stride stance; and the ability to swing the arms and coordinate with the leg pattern. The dynamic component of the algorithm included: independence with hip, knee and ankle flexion; the pelvis rotating properly and symmetrically; weight shift; kinematics for swing, stance and transitions; inter-limb coordination and symmetry; and timing. If the performance on any of these components was considered unsatisfactory, the effect of verbal cueing was tested, followed by the effect of physical facilitation. Based on these outcomes, decisions were made regarding the patient's ability to complete BWSTT, and whether the amount of BWS and assistance provided required modification.

In broad terms, Hornby, Zemon and Campbell (2005) consider that transition from robotics to BWSTT can be attempted when patients are able to generate normal stepping kinematics with upright posture and assistance of only one therapist. The three SCI case studies presented by Hornby, Zemon and Campbell (2005) indicated a process of multiple attempted trials of BWSTT, whereby robotic therapy was continued for the remainder of the session if patients could not sustain an upright posture or normal kinematics during the trial of BWSTT. Hornby, Zemon and Campbell (2005) retrospectively reviewed the following outcome measures for each participant at study entry, on successful transition from the robotic to BWSTT, and at BWSTT completion: Lower Extremity Motor Score (LEMS) of the ASIA scale, 10-metre walk test, six-minute walk test, FIM motor, Walking Index for Spinal Cord Injury (WISCI) II, gait speed, gait endurance, Timed Up and Go (TUG), and Functional Reach in sitting or standing. The three presented SCI patients were able to successfully transition to BWSTT when BWS was 43%, 29% and 12-37% with assistance from one person only. Furthermore, BWSTT transition was successful when FIM motor ambulation score was greater than or equal to four. That is, the patient provided more than 75 per cent of the effort to ambulate 50 metres, or using the household exception of no assistance but only 17 metres achieved. Similar to the multi-component algorithm presented by Backus and Tefertiller (2008), Hornby, Zemon and Campbell (2005) considered that while factors such as the amount of BWS provided, or improvement in LEMS and postural stability, may all contribute to the ability to terminate the robotic, these items are not necessarily able to be used as individual criteria to determine successful transition to BWSTT. Furthermore, the authors indicate that whilst overall walking ability is more relevant to BWSTT ability, the TUG and WICSII may be even less indicative of an ability to terminate the robotic. Gait speed and endurance were proposed as potentially more relevant, however results were based on an arbitrary goal of achieving 1000 metres for one hour in order to be considered successful at BWSTT, which is a large amount of BWSTT. Similar to the concept presented by Backus and Tefertiller (2008), Hornby Zemon & Campbell 2005 also suggests that, when the need for assistance is high, patients might require guided robotic assistance to practice correct kinematics with a proposed transition to BWSTT when having achieved greater volitional control.

To date, none of the proposed algorithms developed for SCI are known to have been applied to stroke, with the potential that this may not be appropriate due to the bilateral and more global deficits found in SCI. As such, specific work relevant to stroke is likely required in order to develop an algorithm for the progression of Lokomat® training to BWSTT in stroke, as recommended by Manickavasagam et al. (2015).

1.15 Literature Review Summary

In summary, the key points from the literature review are that:

- Stroke continues to be a significant problem in Australia, with low CV fitness post-stroke a prominent issue limiting participation in activities and independence.
- For patients with stroke in subacute rehabilitation, the National Stroke Guidelines recommend 30 minutes (in minimum blocks of 10 minutes) of moderate intensity CV exercise defined as 40-60% VO_2reserve, 3-6 MET, or 3-4 points on the BORG CR-10 scale.
- Current conventional therapy does not meet the above recommendations, such that low CV fitness is known to persist from the subacute to chronic phase post-stroke.
- Functional task-specific walking activities for CV exercise are preferable, but difficult to achieve in mobility-dependent patients post-stroke. Assistive technology such the Lokomat® robotic may assist, however the intensity of exercise achieved on robotics is questionable, and passive over-assistance without step-variability may be an issue.
- The APF activities of the Lokomat® which are commonly used for motivation, enjoyment and feedback of patient activity, may assist in increasing CV workload.
- More challenging Lokomat® settings may also increase the CV workload achieved.
- The BORG RPE scale may be useful in a clinical setting to monitor overall and leg workload, if appropriate to be used.
- BWSTT is a known option for CV exercise for patients with stroke who can appropriately complete this, without likely risk of reinforcement of poor gait biomechanics.
- Potential benefits of BWSTT include greater stepping variability and less risk of passive over-assistance however, criteria to guide clinical decision-making for transition from the Lokomat® to BWSTT in stroke are unknown. Broad criteria of severity of impairment, the assistance required, and degree of volitional control may be relevant.

The aims of the current study therefore were:

1. To determine: Can the Lokomat®, with use of the APF activities, be used to complete sustained moderate intensity CV exercise in patients with subacute stroke?
    a. Can a moderate intensity level of CV exercise be achieved using the APF activities?
    b. Is there a difference in the intensity achieved between different APF activities used?
    c. Can moderate intensity CV exercise be sustained for a minimum 10-minute duration?
    d. Do clinical changes in Lokomat® device settings influence the CV workload achieved?

e. Does participant motivation and enjoyment influence CV workload outcomes?
f. Can the BORG CR-10 scale be used clinically to ascertain intensity levels while completing APF activities on the Lokomat®?

2. To develop an algorithm and propose a clinical decision-making tool guiding progression from the Lokomat® to BWSTT in subacute stroke, based on criteria supporting the concepts of patient severity, amount of assistance required, and degree of volitional control.

2. ARTICLE 1
USING AUGMENTED PERFORMANCE FEEDBACK ACTIVITIES DURING LOKOMAT® THERAPY RESULTS IN MODERATE INTENSITY CARDIOVASCULAR EXERCISE IN ADULT PATIENTS WITH SUBACUTE STROKE

2.1 Abstract:

Background: Stroke precedes low CV fitness reported to limit successful participation in activities. Conventional subacute stroke rehabilitation does not meet the National Stroke Guidelines for CV exercise, particularly in mobility-dependent patients. The Lokomat® robotic potentially provides a way to achieve CV exercise with these patients.

Aim: To determine whether moderate intensity CV exercise can be achieved using the APF activities of the Lokomat® in mobility-dependant adults with subacute stroke.

Methods: Ten subacute patients with stroke, mean (SD) age of 63.4 (13) years, participated in six 20-minute Lokomat® study sessions. Each study session they completed, in randomised order, three APF activities, five minutes each. Metabolic data was collected using the COSMED K5®. Participants rated their perceived exertion on the BORG CR-10 scale and Lokomat® settings were recorded.

Results: Moderate intensity CV exercise was achieved in all three Lokomat® APF activities, demonstrated with a mean (SD) VO_2 of 8.0 (3.8) ml/kg/min (estimated 52% VO_2max) and mean (SD) MET of 3.1 (1.3). This was supported by BORG scores between 3 and 5. VO_2 and MET were not affected by type of APF activity (p=0.110 and 0.240) and VO_2, MET, and BORG results were maintained over 15 minutes. Although Lokomat® settings significantly progressed between study sessions ($p<0.05$) as per clinical practice, no significant changes in VO_2 or MET were observed over the six study sessions (p=0.380 and 0.527).

Conclusions: The Lokomat® APF activities, while maintaining clinically optimal device settings, can be used to achieve moderate intensity CV exercise in mobility-dependant adult patients with subacute stroke, in line with recommended guidelines.

Keywords: subacute stroke, robotics, Lokomat®, cardiovascular / aerobic, exercise

2.2 Introduction:

More than 33,300 hospitalisations and 25,800 rehabilitation hospitalisations occurred following stroke in Australia in 2009-10 (AIHW, 2013), with 20-30% of inpatient rehabilitation stroke patients classified as more severely physically disabled (AROC, 2017). Patients with subacute and chronic stroke commonly display approximately 50% of the aerobic capacity of age and gender matched, sedentary but healthy individuals (Smith et al., 2012). This limits their endurance in community ambulation (Barclay et al., 2015), ability to counteract the high energy demand of the hemiplegic gait (Delussu et al., 2014), participation in ADL's (Michael et al., 2005), and independence (Shephard, 2009). Most people post-stroke have a maximal oxygen uptake below the required fitness level (18ml/kg/min) recommended for independence (Marsden et al., 2013).

The Stroke Foundation Clinical Guidelines (Stroke Foundation, 2017) recommend subacute stroke rehabilitation includes moderate intensity CV exercise, defined as 40-60% VO_2 reserve, equivalent to 3-6 METs, or a self-rating of 3-4 on the CR-10 BORG scale, sustained over a minimum 10 minutes (American College of Sports Medicine, 2014; Billinger et al., 2014; Norton, 2010). Despite this, low levels of CV exercise intensity and dosage are reported in conventional therapy (Kaur et al., 2012; Prajapati et al., 2013), with particular challenges observed in mobility-dependent subacute patients with stroke (Billinger et al., 2014; Billinger et al., 2012b; Lefeber et al., 2016; Stoller et al., 2015). When attempted, CV exercise can increase CV fitness in subacute stroke (Sandberg et al., 2016). Evidence favours functional task-specific walking activities (Saunders, Sanderson, Brazzelli, Greig, & Mead, 2013), which are difficult to achieve, particularly for mobility-dependent patients with stroke, in conventional gait rehabilitation.

Previously well described (Riener et al., 2010), the Lokomat® (Hocoma, AG, Switzerland) exoskeleton robotic, where inbuilt sensors monitor and represent active effort in the device's APF activities, has demonstrated effectiveness in improving ambulation for mobility-dependent (FAC <4) patients with subacute stroke (Mehrholz et al., 2017b). Recent investigation in this population includes whether greater CV workloads result from decreased BWS or GF, or increased speed (Lefeber et al., 2016; Schindelholz et al., 2014; Stoller et al., 2013; van Nunen et al., 2012). Despite evidence supporting some change in CV fitness in subacute patients with stroke following up to four weeks of Lokomat® training (Chang et al., 2012; Stoller et al., 2015), current literature suggests low intensity CV training (<40% VO_2 reserve) while on the Lokomat® or other robotics (David et al., 2006; Delussu et al., 2014; Lefeber et al., 2016; Stoller et al., 2015; van Nunen et al., 2012). However, the majority of studies have focussed on feasibility, reliability, and repeatability of the Lokomat® for CPET utilising specially designed software programs, rather than the standard

APF activities of the Lokomat® (Schindelholz et al., 2014; Stoller et al., 2014a; Stoller et al., 2015; Stoller et al., 2013; Stoller et al., 2014b).

The APF activities are used clinically to enhance motivation and enjoyment while providing feedback on, and encouragement for, sustained and heightened lower limb activity. Using the APF activities may reduce concerns regarding non-use of the affected leg when increasing CV work (Stoller et al., 2015), and provide enhanced CV training via a virtual feedback environment (Koenig et al., 2011). The effect of the Lokomat's® own APF activities on CV workload has not been studied to date. Therefore, the primary aim of this research was to determine, in the subacute mobility-dependent adult patient post-stroke, whether sustained moderate intensity CV exercise could be achieved using the APF activities of the Lokomat®. Additionally, this study aimed to assess if CV workload was influenced by the type and order of the APF activity completed, patient motivation and enjoyment, and the clinical progression of device settings.

2.3 Materials/Methods:

Inpatients from a rehabilitation hospital in Adelaide were eligible for inclusion if they were over 18 years old with a recent (between one week and 3 months) diagnosis of stroke, able to follow English instructions and provide written consent as tested with the Mini Mental State Examination (MMSE) >23/30 (Dick et al., 1984) or equivalent, and had completed at least one 20 minute Lokomat® therapy session, with dependent overground mobility defined as receiving a FAC (see Appendix 4) below 3 (FAC<3) (Mehrholz et al. 2017b). Patients were excluded if a prior medical condition precluded them from CV exercise, the Lokomat®, or standard CV exercise testing. Ethical approval for this study was obtained through the Southern Adelaide Clinical Human Research Ethics Committee (HREC/17/SAC/198) (see Appendix 1: Ethics, Participant Information Sheet and Consent).

In each of six study sessions, completed on available consecutive weekdays over two weeks, participants completed the Lokomat® Pro (see Appendix 2: Equipment) version 6 software APF activities of Faster, Graph, and Gabarello 2 (Figure 1), in a computer generated randomised order accounting for all possible order permutations. The three APF activities were chosen due to their low cognitive complexity and use with a wide variation of GF, with all study sessions completed by the same advanced Hocoma trained physiotherapist. At the start of each study session, a five-minute warm up facing a mirror to establish correct orthosis position and a safe physiological gait pattern with the lowest possible GF and BWS, and maximal self-selected speed, was initially

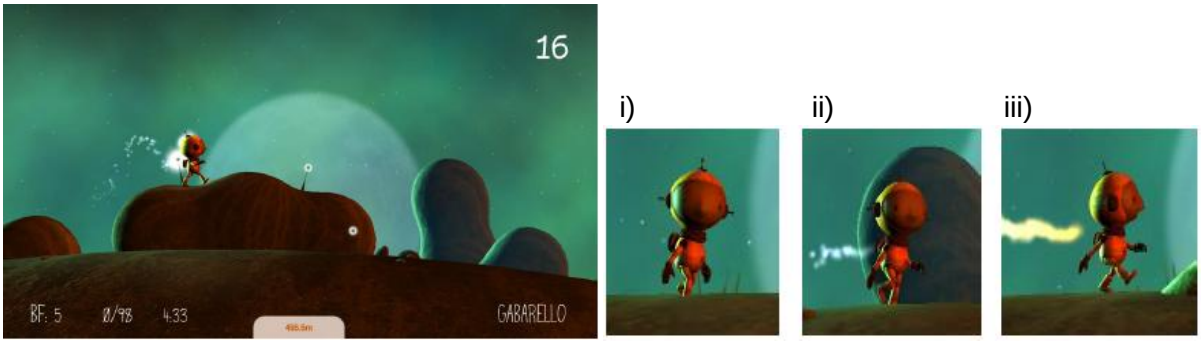
completed. Following this, the Lokomat® functioned continuously on the same settings while each APF activity was completed for five minutes (APF activity block) on a bilateral-limb biofeedback setting, without rest between the three APF activity blocks. As this formed part of an active rehabilitation program, the Lokomat® settings of GF, BWS, and speed were based on clinical judgement of maximum possible therapy progression while maintaining a physiological gait pattern, and recorded each study session.

Figure 1: Augmented Performance Feedback Activities: (Picture: Hocoma, AG, Switzerland)

a) Faster = race against the silver robot for coins

b) Graph = biofeedback units of leg activity

c) Gabarello 2 = collect flowers, power jet pack: leg activity i) low, ii) moderate, iii) high



A five-minute resting metabolic data set was collected prior to each Lokomat® study session using the calibrated COSMED K5® portable metabolic unit (COSMED Srl, Italy) (see Appendix 2), previously demonstrating reliability in stroke (Stookey et al., 2013). Metabolic data was continuously recorded during each study session, and the fourth minute of data for rest and each APF activity block was analysed to ensure a steady state was achieved per APF activity. At the end of the fourth minute of each APF activity block, participants answered the specific questions "how hard is your breathing working?" (BORG-D) and "how hard is your affected leg working?" (BORG-L) using the BORG CR-10 scale (see Appendix 2) as previously recommended (Borg & Kaijser, 2006; Pageaux, 2016) and used in stroke (Sage et al., 2013). Participants also indicated their levels of motivation and enjoyment for each APF activity on a self-created five-point Likert scale (see Appendix 2). Verbal therapist encouragement was used only when necessary to maintain quality of the physiological gait pattern, with GF and BWS purposely reduced between each study session as per usual clinical practice.

From the full suite of metabolic data, VO_2 in ml/kg/min, the gold standard (Smith et al., 2012) was analysed, since HR is less advisable in a CV population where HR may not correlate to VO_2 (David et al., 2006; Krewer et al., 2007; Smith et al., 2012). MET was calculated as a within participant comparison of working oxygen consumption measured during completion of the APF activities divided by resting oxygen consumption measured in sitting prior to each study session. Moderate intensity CV work was defined as 40-60% VO_2 reserve, equivalent to a MET value of 3 or greater, and a self-rating between 3 and 4 on the BORG CR-10 scale, sustained over a minimum 10-minutes (American College of Sports Medicine, 2014; Billinger et al., 2014; Norton, 2010). The minimum 40% VO_2 reserve equates to a VO_2 during APF activities of greater than 6.2ml/kg/min, based on previous literature with a similar population on the Lokomat® (Stoller et al., 2014a). All demographic and outcome measure data was assessed to confirm normal distribution. To assess if CV workload was influenced by (1) the type of APF activity completed, (2) the order in which the

APF activity blocks were completed each study session, and (3) time over the two weeks (including the progression of Lokomat® settings between study sessions), separate repeated measures ANOVAs with post-hoc pairwise comparisons, using Bonfenorri corrections for between study session comparisons, were conducted on VO_2, MET, BORG and Lokomat® settings. Friedman's ANOVA was used for the Likert scale measures of motivation and enjoyment. A Pearsons correlation was completed for VO_2 and BORG CR-10 outcomes. All analyses were completed in SPSS v22 (IBM, Chicago), and alpha was set at 0.05.

2.4 Results:

Ten eligible participants provided written consent between September 2017 and January 2018. Nine participants completed all six study sessions within 12 calendar days. One participant completed two study sessions before knee pain, only present on the robotic device while attempting study session three and without apparent knee pathology or possible device adjustment solutions being found, prevented ongoing use of the Lokomat®. As such, 10 participants (demographics in Table 1) completed 56 of 60 study sessions, and 168 of 180 APF activity blocks were collected and analysed. Overall, participants achieved a mean VO_2 of 8.0 +/-3.8 (CI:7.0-9.0) ml/kg/min, MET of 3.1 +/-1.3 (CI:2.8-3.5), BORG-D 3.5 +/-1.7 (CI:3.1-4.0) and BORG-L 4.8 +/-1.7 (CI:4.4-5.2), with a motivation and enjoyment score of 4 (IQR: 4-5, 3-5 respectively) (see Appendix 3: Results – Grand Means Summary and Post-Hoc Results).

Table 1: Participant Demographics

Age (y)	63.4 +/-13
Male/Female	8 / 2
Time post stroke (d)	32 +/-24
Isch/Haem	7 / 3
Hemi side: R / L	6 / 4
BMI	26.9 +/-4
FAC	0

Isch = Ischaemic, Haem = Haemorrhagic, R = Right, L = Left, BMI = Body Mass Index, FAC = Functional Ambulation Category, Age/Time post stroke/BMI = mean +/- Standard Deviation

The type of APF activity completed (Table 2) did not influence the objective (VO_2/MET) measures of CV workload or perceived affected leg work (BORG-L). A post-hoc pairwise comparison for BORG-D revealed a statistically greater perception of breathing (p=0.013) for the Faster APF as compared to Gabarello 2 (see Appendix 3 for post-hoc details). Motivation was unaffected by the

choice of APF activity, however participants rated enjoyment of the Graph higher than either Faster (p=0.004) or Gabarello 2 (p=0.007) on post-hoc analysis.

Table 2: Effect of Type of Augmented Performance Feedback Activity Completed on VO_2, MET, BORG, Motivation and Enjoyment

Outcome	Faster	Graph	Gabarello 2	*p* value
VO_2 (ml/kg/min)	8.1 +/-3.9 (CI:7.1-9.2)	7.9 +/-3.5 (CI:6.9-8.8)	8.0 +/-3.9 (CI:7.0-9.0)	0.110
MET	3.2 +/-1.3 (CI:2.8-3.5)	3.1 +/-1.2 (CI:2.8-3.4)	3.2 +/-1.4 (CI:2.8-3.5)	0.240
BORG-D	3.8 +/-1.7 (CI:3.3-4.3)	3.5 +/-1.8 (CI:3.0-4.0)	3.3 +/-1.6 (CI:2.9-3.8)	0.044*
BORG-L	5.1 +/-1.8 (CI:4.6-5.6)	4.7 +/-1.6 (CI:4.2-5.1)	4.7 +/-1.8 (CI:4.2-5.2)	0.115
Motivation	4 (3-5)	4 (4-5)	4 (4-5)	0.070
Enjoyment	4 (2.8-4)	4 (4-5)	4 (3-4)	0.000*

n=56 sessions/10 participants, *= significant result (p=0.05), VO_2/MET/BORG = mean +/- Standard Deviation (CI=Confidence Interval 95%), Motivation/Enjoyment = median (1^{st}-3^{rd} IQR)

The order in which the APF activities were completed within each study session did not affect the objective measures of CV workload (VO_2/MET) (Table 3). However, a statistically significant difference was found for both BORG-D and BORG-L. Post-hoc pairwise comparisons revealed significantly lower BORG scores during the first as compared to second completed activity (BORG-D:p=0.014, BORG-L:p=0.046), as well as first to third completed activity (BORG-D:p=0.001, BORG-L:p=0.027) (see Appendix 3 for post-hoc details). Both motivation and enjoyment were unaffected by the order of APF activities.

Table 3: Effect of Order of Augmented Performance Feedback Activity Completion on VO_2, MET, BORG, Motivation and Enjoyment

Outcome	1st	2nd	3rd	*p* value
VO_2 (ml/kg/min)	7.9 +/-3.7 (CI:6.9-8.9)	8.2 +/-3.9 (CI:7.1-9.2)	7.9 +/-3.8 (CI:6.9-8.9)	0.250
MET	3.1 +/-1.3 (CI:2.8-3.5)	3.2 +/-1.4 (CI:2.8-3.6)	3.1 +/-1.3 (CI:2.8-3.5)	0.703
BORG-D	3.2 +/-1.6 (CI:2.7-3.6)	3.7 +/-1.6 (CI:3.2-4.1)	3.8 +/-1.8 (CI:3.3-4.3)	0.003*
BORG-L	4.5 +/-1.7 (CI:4.0-5.0)	5.0 +/-1.7 (CI:4.5-5.4)	5.0 +/-1.7 (CI:4.5-5.5)	0.043*
Motivation	4 (4-5)	4 (4-5)	4 (4-5)	0.889
Enjoyment	4 (3-5)	4 (3-5)	4 (3-5)	0.646

n=56 sessions/10 participants, *=significant result (p=0.05), VO_2/MET/BORG = mean +/- Standard Deviation (CI=Confidence Interval 95%), Motivation/Enjoyment = median (1^{st}-3^{rd} IQR)

There were no significant changes in VO_2, MET, BORG, motivation or enjoyment over the six study sessions (Table 4), despite the Lokomat® settings demonstrating significant between-session differences for BWS (p=0.003) and GF (p=0.005), reduced purposely between study sessions as part of therapy progression (see Appendix 3 for post-hoc details). Resting measures of VO_2 (p=0.829), BORG-D (p=0.845), and BORG-L (p=0.336) were consistent across study sessions and weak statistical correlations were found between VO_2 and both BORG-D and BORG-L (see Appendix 3).

Table 4: Effect of Session Order on VO_2, MET, BORG, Motivation and Enjoyment

Outcome	S1	S2	S3	S4	S5	S6	*p* value
VO_2	7.6 +/-3.3 (5.1-10.1)	7.7 +/-3.4 (5.2-10.3)	7.5 +/-3.4 (4.9-10.1)	7.8 +/-3.9 (4.8-10.8)	8.1 +/-4.2 (4.9-11.3)	7.7 +/-3.8 (4.8-10.6)	0.380
MET	2.9 +/-0.9 (2.2-3.6)	3.1 +/-0.9 (2.4-3.8)	3.4 +/-1.6 (2.2-4.7)	3.1 +/-1.4 (2.0-4.2)	2.9 +/-1.0 (2.1-3.7)	2.7 +/-0.9 (2.0-3.5)	0.527
BORG-D	3.3 +/-1.4 (2.2-4.4)	3.2 +/-1.4 (2.2-4.3)	3.3 +/-1.4 (2.2-4.4)	3.4 +/-1.1 (2.6-4.3)	3.8 +/-1.6 (2.6-5.0)	4.0 +/-1.8 (2.6-5.4)	0.386
BORG-L	4.7 +/-1.2 (3.7-5.6)	4.1 +/-1.6 (2.9-5.4)	5.1 +/-1.4 (4.1-6.2)	5.0 +/-1.7 (3.7-6.3)	5.3 +/-1.4 (4.2-6.4)	4.4 +/-1.7 (3.2-5.7)	0.386
Motivation	4 (3.7-4.7)	4 (3.7-4.7)	4 (4.0- 4.7)	4 (3.7-5.0)	4 (3.7-5.0)	4 (3.3-4.3)	0.188
Enjoyment	4 (3.3-4.3)	4 (3.0-4.3)	4 (3.3-4.3)	4 (3.3-4.3)	4 (3.7-4.3)	4 (2.7-4.3)	0.513
BWS	39.3+/-7.7 (33.4-45.3)	37.0 +/-7.1 (31.5-42.5)	35.0 +/-7.6 (29.2-40.1)	32.8 +/-7.4 (27.1-38.4)	32.4 +/-7.5 (26.7-38.2)	31.2 +/-8.3 (24.9-37.6)	0.003*
GF	55 +/-13.7 (44.5-65.5)	51.5 +/-13.2 (41.3-61.6)	48.9 +/-14.8 (37.6-60.2)	44.4 +/-13.8 (33.8-55.0)	43.3 +/-13.5 (33.0-53.7)	40.6 +/-13.6 (30.1-51.0)	0.005*
Speed	1.7 +/-0.4 (1.4-2.0)	1.8 +/-0.4 (1.5-2.1)	1.9 +/-0.4 (1.6-2.1)	1.9 +/-0.4 (1.6-2.2)	1.9 +/-0.4 (1.6-2.2)	1.9 +/-0.4 (1.6-2.2)	0.122

n=54 sessions/9 participants, *=significant results (p=0.05), VO_2/MET/BORG/BWS/GF/speed = mean +/- Standard Deviation (Confidence Interval = 95%), Motivation/Enjoyment = median (1^{st}-3^{rd} IQR), BWS=Body Weight Support, GF=Guidance Force

2.5 Discussion:

The research aim was to determine whether sustained moderate intensity CV exercise could be achieved using the APF activities of the Lokomat® in mobility-dependent adult patients with subacute stroke. Secondary aims were to assess differences in CV workload according to the type and order of APF activity completion, participant motivation and enjoyment, and clinical progression of device settings between study sessions. The study results demonstrated that using the APF activities of the Lokomat®, mobility-dependent adult patients with stroke in subacute rehabilitation can achieve sustained moderate intensity CV exercise in line with recommended guidelines, irrespective of the particular APF activity completed or participant perspectives towards

activities. Furthermore, maintenance of CV workload was demonstrated with a clinical progression of device settings.

As the CPET modality influences CV outcomes (van de Port et al., 2015) the intensity achieved by participants in the current study was compared with findings reported by Stoller et al. (2014a). In this study, a similar group of patients completed a CPET on the Lokomat® achieving a VO_2 peak of 15.5 +/-4.9 ml/kg/min. When compared to a pooled mean VO_2 of 8.0 +/-3.8 ml/kg/min in the current study, this demonstrates an equivalent intensity of 52% VO_2max, which is enough to meet criteria for moderate intensity CV exercise (American College of Sports Medicine, 2014; Billinger et al., 2014; Norton, 2010). Moderate intensity is further supported by current study participants achieving a within participant MET of 3.1 +/-1.3, whereby a MET of three to six constitutes moderate intensity CV exercise (American College of Sports Medicine, 2014; Billinger et al., 2014; Norton, 2010). Moreover, the mean self-perceived BORG score of 3.5 +/-1.7 for BORG-D and 4.8 +/-1.7 for BORG-L confirmed participants were exercising at a moderate intensity, considering that clinically a range of 3 to 4 on the CR-10 BORG scale represents moderate intensity (American College of Sports Medicine, 2014; Borg & Kaijser, 2006; Norton, 2010).

The type of APF activity completed did not influence the objective intensity measures (VO_2/MET), or the subjective perception of affected leg work (BORG-L). Participants did perceive a higher effort of breathing (BORG-D) in the Faster APF activity as compared to the Gabarello 2 activity, which may be explained by the interval-based repetitive short-burst race against a competitor/computer controlled avatar environment of the Faster APF. This is supported by the knowledge that visual stimulus can affect HR (Riedo & Hunt, 2017) and hence potentially perception of exertion (Borg, 1982). Comparatively, while the Gabarello 2 APF activity is a visual media, it provides a more constant stimulus without consecutive racing intervals as compared to the Faster APF activity. Motivation was not influenced by the type of APF activity, although participants did report higher enjoyment of the Graph APF, consistent with variances regarding feedback used in other studies (Banz, Bolliger, Colombo, Dietz, & Lünenburger, 2008; Lunenburger, Colombo, Riener, & Dietz, 2004). As the objective workload did not vary from the type of APF activity completed, participant choice and clinician recommendation can occur without losing the CV training effect.

Whilst objective CV workload measures were maintained equally over the 15 minutes, perceived effort of breathing and leg work increased following the APF activity completed first. This further

supports that intensity and duration criteria for moderate intensity CV exercise was achievable with an increasingly perceived but sustainable challenge. This sustained CV intensity, without significant fatigue, and no loss of motivation or enjoyment, is important because previous stroke research has demonstrated inability to sustain overground walking to meet CV exercise criteria (David et al., 2006; van Nunen et al., 2012). This result also adds support towards robotics for duration and endurance training (Krewer et al., 2007; Lefeber et al., 2016).

Lokomat® settings in the current study were purposely progressed according to clinical practice between the six study sessions, resulting in significant differences for BWS and GF, but not self-selected speed. The decreased BWS and GF did not, however, equate to significantly higher CV workloads as measured either objectively (VO_2/MET) or subjectively (BORG D and L), and did not affect motivation or enjoyment. Whilst this may seem contradictory to the literature, which suggests lower BWS and GF causes a higher CV workload, variability in prior results exists, and a much greater reduction in device settings has been used in prior studies than would clinically be possible in the mobility-dependent cohort in the current study (David et al., 2006; Delussu et al., 2014; Krewer et al., 2007; Lefeber et al., 2016; Schindelholz et al., 2014; Stoller et al., 2013; van Nunen et al., 2012). Another explanation may be improvement in participants' aerobic capacity over the six sessions completed over eight to 12 days, consistent with a finding from Chang et al. (2012) where participants' CV capacity improved after two weeks of Lokomat® therapy. This could mean the same objective and subjective result was achieved by "fitter" participants on more challenging device settings, consistent with results from a previous study (Macko et al., 2001) and highlighting the need to adjust Lokomat® settings according to participant improvement.

This study has some limitations for consideration. It was completed as a measure of clinical practice comparing only three of the available APF activities within a subacute rehabilitation facility whereby Lokomat® device settings were adjusted in line with clinical practice. As such, no control group was used, and no measures of VO_2 max were completed on this specific cohort which would have strengthened results. Potential for bias by the principle investigator also being the primary treating Lokomat® therapist at the facility and non-blinding is acknowledged, however, standardised clinical treatment protocols and specific questions for the BORG scale and Likert scale were used, as well as objective measures for CV workload that were not observed by the investigator throughout the study. The study included only 10 participants, however, the study design allowed for the analysis of 60 study sessions including 180 APF activities. Repetition of the study with a larger sample size is proposed and would strengthen the study conclusions across a broader range of participants.

2.6 Conclusion:

In clinical therapy at the lowest possible BWS and GF, and highest self-selected speed, using APF activities in Lokomat® robotic-assisted gait training, results in moderate intensity CV exercise. Clinician choice and patient's preference of APF activity is appropriate, with maximised device settings used and continually progressed to meet CV exercise guidelines. Further research into APF activities designed specifically for this purpose is warranted.

3. ARTICLE 2
TOWARDS THE DEVELOPMENT OF A CLINICAL DECISION-MAKING TOOL GUIDING THE TRANSITION BETWEEN LOKOMAT® AND BODY-WEIGHT SUPPORTED TREADMILL TRAINING IN PATIENTS WITH SUBACUTE STROKE: AN EXPLORATIVE STUDY.

3.1 Abstract:

Background: Contemporary post-stroke subacute locomotor rehabilitation typically includes robotics or BWSTT. Advantages and disadvantages, as well as ongoing conflicting evidence of efficacy, exist between these two modalities. Questions therefore remain regarding the choice of modality throughout the subacute rehabilitation journey.

Aim: To develop a proposed clinical decision-making tool guiding transition from the Lokomat® to BWSTT in adult patients with subacute stroke.

Method: For ten adult participants with subacute stroke completing Lokomat® therapy, a clinical judgement was made regarding ability to complete BWSTT. This judgement was compared to: participants' FAC score; clinical evaluation of sit to stand and standing; Lokomat® settings; lower limb biomechanics including maximal active hip and knee flexion in standing and gait biomechanics in BWSTT. An algorithm based on this information was then developed which informed a proposed clinical decision-making tool.

Result: Clinical judgement deemed four of ten participants ready to transition to BWSTT. Unlike participants judged not-ready for BWSTT these participants: a) had a FAC of 1; b) performed sit to stand and standing balance with minimal support and even weight bearing; c) trained with Lokomat® settings: BWS<30%, GF <30-35%, speed >2.0kph; d) had >45 degrees standing active hip and knee flexion; e) had no significant issues with their physiological stepping pattern in BWSTT that could not be controlled with verbal or physical facilitation by one person.

Conclusion: Participants judged ready for BWSTT presented with increased independent functional ability, more challenging Lokomat® settings, greater active volitional lower-limb control, and less issues with physiological stepping in BWSTT. An algorithm and clinical decision-making tool incorporating all of these factors are proposed as preliminary exploratory work in this area.

Key words: Robotics, Lokomat®, BWSTT, body weight support, treadmill, stroke, subacute, progression, transition, algorithm, clinical decision

3.2 Introduction:

BWSTT consists of a form of patient harness suspended over a treadmill to reduce the weight bearing forces of the patient's own body weight through their lower limbs. It aims to provide a safe and supportive way to practice a high dosage of functional, repetitive, task-specific walking post-stroke (Ada et al., 2010a; Backus & Tefertiller, 2008; Hesse, 2008; Hornby et al., 2005). It has also previously demonstrated efficacy in providing CV training in subacute stoke (Mackay-Lyons et al., 2013). The Lokomat® device can be used to provide BWSTT once the robotic orthosis is removed from the patient's limbs, with or without additional manual therapist support. Similar, but to a lesser extent than with the robotic device, the trunk and body weight remain partially supported in BWSTT, but the lower limbs are free of mechanical assistance. As such, the patient needs to work more actively and independently on posture, trunk and pelvis control, balance, lower limb movements, and precision of gait biomechanics (Backus & Tefertiller, 2008). Potential advantages and disadvantages of robotic-assisted versus BWSTT modalities of locomotor training exist, as indicated in Table 5 (Ada et al., 2010a; Backus & Tefertiller, 2008; Backus et al., 2010; Crompton et al., 2001; Hornby et al., 2010; Hornby et al., 2005; Manickavasagam et al., 2015; Westlake & Patten, 2009).

Table 5: Advantages and Disadvantages to Robotic-assisted and Body-Weight Supported Treadmill Training Modalities of Locomotor Training Post-Stroke.

Advantages Robotic	**Disadvantages Robotic**	**Advantages BWSTT**	**Disadvantages BWSTT**
Reduced number of therapists required	Lack kinematic variability for learning	Forced greater patient activation	Potential need multiple therapists
Less physical demand on therapists	Passive dorsiflexion	Lessened/more controllable sensory input	Potential OH&S issues for therapists
Higher dosage repetitive stepping	Speed limitations	Therapist step-step adjustments possible	Less overall duration/ more fatigue
Greater duration therapy	Potential passive over-support	High dosage if matched, or more than overground	Unable to quantify assistance given
More symmetrical stepping	Timely set up	Interval based training	Unable to quantify patient effort
Precision therapy parameters	Expensive initial outlay	Greater variability per step for learning	Difficult with multi component assistance
Precise joint range can be set			Challenges with spasticity
Ability to monitor assistance provided			
Ability to monitor patient effort			
Virtual reality environment			

Given the different advantages and disadvantages of robotic versus BWSTT locomotor therapy, the choice of which modality to use at any stage in a patient's journey, or whether to complete conventional and overground training instead, continues to be difficult, with conflicting research results regarding the use of each modality in stroke (Backus & Tefertiller, 2008; Hornby et al., 2010; Hornby et al., 2005; Mao et al., 2015; Westlake & Patten, 2009). A recent Cochrane review of robotic therapy in stroke suggests that for mobility-dependent patients with subacute stroke with a FAC score less than 4, robotics, in conjunction with conventional therapy is preferential over other forms of therapy alone (Mehrholz et al., 2017b). Furthermore, it was suggested in the Cochrane review that robotics may be less effective for independently ambulating patients. Research regarding improved outcomes following BWSTT in stroke are, however, highly inconclusive. For example, consecutive Cochrane reviews on BWSTT in stroke implied few beneficial outcomes, potentially limited to velocity and endurance only, and possibly only with ambulatory patients (Mehrholz et al., 2014; Mehrholz et al., 2017a; Moseley et al., 2005). Other studies have demonstrated good outcomes in ambulatory patients from aggressive supported overground therapy (Kosak & Reding, 2000) and limited benefit of BWSTT in non-ambulatory patients (da Cunha Jr et al., 2002; Nilsson et al., 2001), bringing into question the efficacy of utilising this modality at all. Conversely, studies demonstrating beneficial outcomes for BWSTT in non-ambulant subacute stroke, such as more independence, and earlier and higher rates of discharge home with greater walking capacity at six months, do exist (Ada et al., 2010a; Ada et al., 2010b; Dean et al., 2010; Mao et al., 2015). Therefore, it may be considered that BWSTT is as effective as other forms of locomotor therapy post-stroke (Franceschini et al., 2009), with repetitive dosage perhaps being the most important factor, regardless of modality choice (Ada et al., 2010a; Behrman et al., 2005; Hornby et al., 2011).

Previous concerns regarding altered gait biomechanics being reinforced by repetitive practice with BWSTT (Hesse, 2008) have been diminished by research demonstrating preferential outcomes for BWSTT regarding improvement in kinematics or spatiotemporal patterns (Brouwer et al., 2009; Hornby et al., 2011; Mao et al., 2015). The improvements from BWSTT are suggested to relate to inherent step variability afforded by this modality and the need to learn through error (Lewek et al., 2009; Manickavasagam et al., 2015). Although there is evidence of some degree of variability per step within the Lokomat® (Hidler et al., 2008), which can be enhanced with the use of the path control feature (Duschau-Wicke et al., 2010), the inherent variability of steps would still be greater and hence more advantageous in non-mechanically guided BWSTT (Backus & Tefertiller, 2008). Moreover, path control can only be used at lower GF settings which are not manageable by all patients.

While acknowledging the ongoing conflicting clinical outcomes, the consideration of an early transition from robotic therapy to BWSTT for emerging ambulators is warranted based on the potential for BWSTT to provide safe high dosage repetitive task-specific practice with spatiotemporal and kinematic variability and reduced chance of passive over-assistance (Ada et al., 2010a; Backus & Tefertiller, 2008; Hornby et al., 2005). However, because of the variability between the evidence regarding clinical outcomes, the advantages and disadvantages of both modalities, and the many factors contributing to individual patients, the clinical decision regarding which modality to use and when to transition someone from a robotic to BWSTT is considered difficult (Backus & Tefertiller, 2008; Hornby et al., 2010; Hornby et al., 2005) or a "grey zone" (Duschau-Wicke et al., 2010).

Evidence based criteria guiding the choice of modality, or the progression from the Lokomat® or other robotics to BWSTT is limited, including a small number of articles on SCI with only small participant numbers in each (Backus & Tefertiller, 2008; Behrman et al., 2005; Hornby et al., 2005). Two of these studies propose clinical decision-making algorithms for adults with SCI regarding the transition from robotic therapy to BWSTT (Backus & Tefertiller, 2008), and progression of BWSTT settings (Behrman et al., 2005), although results need to be interpreted with caution due to low participant numbers. Three broad concepts identified and discussed regarding the choice of modality or progression from robotics to BWSTT are, in order of recommended consideration: the severity of impairment; the amount of assistance required to safely stand and mobilise; and the degree of volitional control in standing and stepping (Backus & Tefertiller, 2008; Behrman et al., 2005; Hornby et al., 2010; Hornby et al., 2005). Currently, the only related recommendation in stroke is that patients with a higher degree of severity, noted as those with a FAC less than 4, should complete the Lokomat® when mobility-dependent and in the subacute stage (Mehrholz et al., 2017a). With no other defined criteria for stroke, Manickavasagam et al. (2015) consider that the use of a clinical decision-making algorithm similar to that developed for SCI by Backus and Tefertiller (2008) may be useful for other conditions such as stroke. As a result of the gap in the literature and evidence, the aim of this study was to complete an exploratory study to develop an algorithm and from that propose a clinical decision-making tool guiding transition from the Lokomat® to BWSTT therapy in subacute stroke.

3.3 Methods:

An observational case series, following a duration of Lokomat® therapy, compared a data set of outcomes between participants clinically judged prior to the data collection as being capable of commencing BWSTT therapy (BWSTT-ready) to participants judged not-capable of commencing BWSTT (not-ready BWSTT). The observational comparison was used to develop an algorithm,

which informed development of a proposed clinical decision-making tool for transition from the Lokomat® to BWSTT in subacute stroke. The choice of outcome measures, as well as the development of both the algorithm and proposed clinical decision-making tool were informed by the previous literature, including the use of three key areas: severity of impairment, assessment of assistance required, and assessment of volitional control. Inpatients from a rehabilitation hospital in Adelaide were eligible for inclusion if they were over 18 years old with a recent (between one week and three months) diagnosis of stroke, able to follow English instructions and to provide written consent (MMSE >23/30 or equivalent), had completed at least one 20 minute Lokomat® therapy session, and had a FAC score (see Appendix 4) below 3 to be defined as mobility-dependent (Mehrholz et al. 2017b). Patients with a prior medical condition that precluded them from CV exercise or the Lokomat® were excluded. Ethical approval for the study was obtained through the Southern Adelaide Clinical Human Research Ethics Committee (HREC/17/SAC/198).

The current study was completed alongside the study reported in Chapter 2, evaluating CV exercise while using the APF activities on the Lokomat® in adult patients with subacute stroke. Incorporated between both studies, participant demographics, including the total number of Lokomat® and BWSTT therapy sessions completed over the participants' subacute inpatient stay, were collected (see Appendix 4: Data Collection Sheet). For the purpose of this observational study, immediately following the last Lokomat® session of the CV exercise study, information and data was collected on the following items represented below against the three areas from the literature, namely severity, assessment of assistance required, and assessment of volitional control. The clinical judgement, data collection and analysis was completed by the same advanced Hocoma trained physiotherapist with 2.5 years experience on the device and 20 years clinical experience with stroke, Practically, and to avoid bias toward the clinical judgement, the clinical judgement was made first, before any other data collection, using subjective clinical observation of the assessment of volitional control described below (item 3a and b) (see Appendix 5: Participant Flow). The clinical judgement of readiness was defined as participants during BWSTT being able to sustain a physiological gait pattern at less than the recommended 50% BWS (Hesse, 2008) for one minute with support from only one therapist. One minute was considered as the minimum sensible time to complete intervals of BWSTT, and recommendations have previously been made to complete robotic therapy if more than one therapist is required (Hornby et al., 2005). Subsequent to the clinical judgement, outcomes for the remaining items were measured and recorded, including the objective video measurement of biomechanics of items 3a and b, for comparison to the pre-determined clinical judgement. All participants had the first two items collected and were assessed regarding item 3a which informed the collection of 3b as described below.

1. Participant Severity: Participants' FAC score and ward mobility as per ward clinician.

2. The amount of assistance required:
    a. Clinical observation of the assistance required by the participant while completing the functional tasks of sit to stand, standing balancing, and evenness of weight-bearing during the fitting of the BWS harness at device set-up.
    b. The Lokomat® settings: BWS, GF, and speed.
3. The amount of volitional control:
    a. A repeated active “standing affected-leg lift” (SALL) test (a self-designed test to indicate volitional active maximal hip and knee flexion in standing) was attempted/completed at less than 50% BWS after the orthosis of the Lokomat® was removed. Participants with minimal to no observed active movement were recorded as unable to attempt the SALL test, did not have video collected, did not progress onto the BWSTT trial described below, and were automatically clinically judged as not-ready for BWSTT therapy at this point. For remaining participants, a judgement was made from observation of the completed SALL test regarding ability to attempt the BWSTT trial described below. Subsequently, mean joint angles of maximum active standing affected-leg hip and knee flexion and ankle dorsiflexion were determined from sagittal plane video collected on five maximal leg lifts using the P&O Clinical Movement Data system (version 2.1.0.8, P&O Data Solutions in partnership with the Tarn Group Limited, NZ) with a compatible camcorder (Panasonic HC-V550M, Panasonic Corporation, Australia) (see Appendix 2 and Figure 2).
    b. A BWSTT trial was completed for participants clinically considered in the SALL test as having enough active voluntary affected limb movement to warrant a dynamic trial of BWSTT. The clinical judgement regarding the participant being ready or not-ready for BWSTT therapy was made during observation of the BWSTT trial . The BWSTT trial was captured in the P&O Clinical Movement Data system (see Appendix 2) and subsequently, hip, knee and ankle kinematics at terminal extension, toe off, mid-swing, terminal swing, and mid-stance, as well as foot contact position, spatiotemporal measures, and BWSTT settings were measured from the BWSTT trial. Mean joint angles and spatiotemporal measures (as listed in Table 8) were determined from sagittal plane video based on nine gait cycles (affected toe-off to affected toe-off). The amount of BWS provided was minimised, aiming for less than the recommended 50% (Hesse, 2008) while still maintaining knee control in stance. A participant self-selected comfortable speed was used.

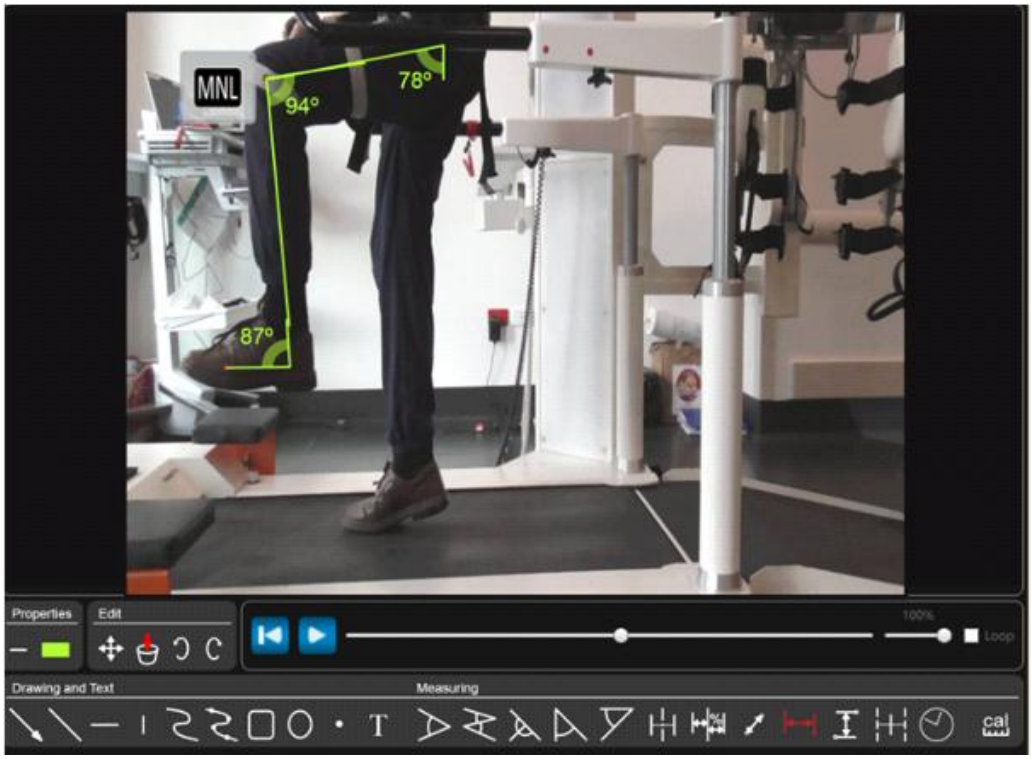
Adhesive markers were placed laterally over the affected limb greater trochanter, centre-mid thigh/femoral line, knee/mid-tibial plateau, lateral malleolus and on the shoe at the head of the fifth metatarsal as consistent reference points for use in the video analysis of the above SALL test and

BWSTT trial. Two adhesive markers were placed 10cm apart on the Lokomat® frame to allow calibration of distance within the P&O software for speed and distance measurements.

Analysis:

An observational comparison of FAC and ward mobility, clinical observations of sit to stand, standing balance and weight bearing ability, and Lokomat® settings was completed between participants clinically judged as BWSTT-ready and participants clinically judged not-ready for BWSTT. Additionally, for participants able to attempt the SALL test, and/or BWSTT trial, BWSTT settings, joint kinematics, and spatiotemporal parameters were compared. The split of data outcomes between the participants judged ready and not-ready for BWSTT was then used in an algorithm against the areas of severity, assessment of assistance required, and assessment of volitional control. The algorithm informed development of a proposed clinical decision-making tool recommended for future testing of validation and potential practical use.

Figure 2: P&O Clinical Movement Data Analysis



3.4 Results:

Participant Characteristics:

Participant characteristics, Lokomat® and BWSTT usage during participant's subacute inpatient stay are presented in Table 6. Of the 10 participants who were mostly male (8:2), with ischemic

stroke (7:3), four were clinically judged as being ready to progress to BWSTT therapy (P4,6,7,9). Six were clinically judged as not-ready for BWSTT therapy (P1,2,3,5,8,10). Participants clinically judged as not-ready for BWSTT therapy tended to have completed more sessions on the Lokomat® prior to commencing the study and rarely progressed to BWSTT for the remainder of their subacute inpatient stay. These not-ready for BWSTT participants were noted also to have had a greater duration since stroke onset and included all of the haemorrhagic presentations.

Table 6: Participant Characteristics, Lokomat® and Body-Weight Supported Treadmill Training Use During Inpatient Subacute Rehabilitation

Participant Number	Age (yrs)	Gender	Days since stroke	Stroke Type	Hemi side	Number Lokomat sessions pre-review	Number Lokomat sessions post-review	Number BWSTT sessions post-review	FAC at study consent
1	50	Male	80	Haemorrhagic	Right	25	18	0	0
2	68	Male	21	Ischaemic	Left	10	22	0	0
3	63	Male	30	Haemorrhagic	Right	14	16	0	0
4	**69**	**Male**	**11**	**Ischaemic**	**Left**	**10**	**0**	**12**	**0**
5	81	Female	44	Ischaemic	Left	11	4	0	0
6	**81**	**Male**	**20**	**Ischaemic**	**Left**	**10**	**0**	**5**	**0**
7	**69**	**Female**	**8**	**Ischaemic**	**Right**	**4**	**0**	**22**	**0**
8	62	Male	22	Ischaemic	Left	13	29	0	0
9	**47**	**Male**	**19**	**Ischaemic**	**Right**	**11**	**3***	**8**	**0**
10	44	Male	67	Haemorrhagic	Left	18	21	0	0

Participant 4,6,7,9 in bold as ready for BWSTT. *Participant 9, following the clinical decision to be BWSTT-ready, completed three split sessions combining use of both the Lokomat® and BWSTT per therapy session to maximise dosage, intensity, and endurance at a higher speed on the robotic.

Participant Severity:

As per Table 7, the six participants clinically judged as not-ready for BWSTT (P1,2,3,5,8,10), according to their ward therapist assessment, mostly needed two people and the rail to assist them for ward mobility, therefore receiving a lower FAC of 0. Conversely, the four participants (P4,6,7,9) who were clinically judged as being ready for BWSTT were mostly reported as completing overground mobility with less assistance away from a rail and hence typically had a FAC of 1 (see Table 7). Assessment of the severity of the mobility deficit, as the first section of the algorithm and proposed clinical decision-making tool (Figure 3a and 3b), therefore included the result that people requiring assistance from two therapists and a rail or with a FAC of 0 continue on the Lokomat®. Conversely, the first section of the algorithm and proposed tool includes that people completing overground mobility with assistance from one therapist and a FAC of 1 move onto an assessment

of the assistance required as the next section of the algorithm and proposed clinical decision-making tool.

Assessment of Assistance Required – Clinical Observations

Two comparisons between BWSTT-ready and not-ready participants contributed to the assessment of the assistance required. Firstly, clinical observation of the assistance required to complete sit to stand and standing with even weight-bearing during fitting of the BWS harness, and secondly assistance required from the Lokomat® settings reported below. Overall, the six participants clinically judged as being not-ready for BWSTT therapy needed physical assistance from at least one therapist for sit to stand and standing balance, and did not weight-bear evenly or at all on the affected leg in standing (Table 7). The four participants clinically judged as ready for BWSTT therapy needed no physical assistance for sit to stand and stood easily with equal weight distribution across both legs. Assessment of the assistance required was added as the second section of the algorithm and clinical decision-making tool, firstly including the observations of the assistance required to complete the functional tasks of sit to stand and standing with even weight-bearing. This section of the algorithm and proposed clinical decision-making tool therefore includes that people requiring physical support from one or more therapists for sit to stand, standing balance, or who stand with no or uneven weight-bearing, continue on the Lokomat®. At the same time, people requiring no physical assistance for sit to stand, or standing balance, and who stand with even weight-bearing, are included as needing to undergo further assessment of volitional limb control.

Assessment of Assistance Required - Lokomat® Settings:

The six participants clinically judged as not-ready for BWSTT predominantly had higher Lokomat® BWS and GF settings (>30%BWS, >35%GF), and lower device speed (<2.0kph), as compared to the four participants clinically judged as being ready for BWSTT (Table 7). The Lokomat® settings were added to the second section of the algorithm and clinical decision-making tool, as the other component of the assessment of assistance required. The included results are that people requiring more than 30% BWS, more than 30-35% GF, and a speed lower than 2.0kph continue use of the Lokomat®. Conversely, people with a BWS below 30%, GF below 30-35%, and speed above 2.0kph, are included as needing further assessment regarding their volitional limb control.

Table 7: Ward mobility, Functional Ambulation Category, Standing Ability, Lokomat® Settings and Standing Affected-leg Lift Angles.

Participant	Ward Mobility at Review Session	FAC at BWSTT Review Session	Standing Ability during Harness Fit	Min RAGT BWS (%)	Min RAGT GF (%)	Max RAGT Speed (kph)	SALL Max Hip Flexion	SALL Max Knee Flexion	SALL Max DF
No to BWSTT (n=6)									
No to SALL (n=4)									
1	1-2A Rail	0	1A, non-WB LL	35	50	1.7	unable	unable	unable
5	2A Rail	0	2A, non-WB LL	43	65	1.7	unable	unable	unable
8^	1A Rail/Quad	0/1	SB, non-WB LL	29	30	1.8	unable	unable	unable
10	2A Rail	0	1A, non-WB LL	31	45	1.9	unable	unable	unable
Yes to SALL (n=2)									
2	1-2A Rail	0	1A, uneven-WB LL	36	45	1.7	23	32	-18
3	1A Rail/ 2AQuad	0/1	SB, uneven WB LL	34	40	2.4	42	40	0
Yes BWSTT + SALL (n=4)									
4	1A Quad OG	1	(I),even WB LL	27	30	2.4	69	99	-2
6[#]	2A Frame OG	0/1	SB,even WB LL	25	35	1.3	51	47	-11
7	1A Quad OG	1	(I), even WB LL	32[@]	30	2.0	65	72	6
9	1A Quad OG	1	(I),even WB LL	16	20	2.4	70	87	8
Summary/Average									
No to BWSTT (mean)	1-2A, Rail	0	1-2A, unevenor non-WB LL	35	46	1.87	32	36	-9
Yes to BWSTT (mean)	1A, Quad, OG	1	(I)-SB, even WB	25	29	2.02	64	76	0

FAC = Functional Ambulation Category, BWS = body weight support, GF = guidance force, RAGT = robot assisted gait training (Lokomat®), SALL = standing affected-leg lift, DF = dorsiflexion, BWSTT = body weight supported treadmill training, ^Participant 8: while progressing to overground mobility, needing lower levels of assistance, and lower Lokomat® BWS/GF settings had high tone allowing no dissociated hip/knee flexion and so was unable to complete the SALL test and automatically not-ready for BWSTT. Due to poor quality OG gait they continued use of the robotic for all remaining therapy sessions (Table 2). [#]Participant 6: usual gait pattern included use of a frame, and was pre-morbidly slower, two assistance overground (OG) was due to balance which was assisted by the device in BWSTT. [@]Participant 7: BWS recorded on the 4th Lokomat® session due to knee pain, it is likely the BWS would have been lowered over uncompleted study sessions.

Assessment of Volitional Control - Standing Affected Leg Lift:

Comparison between BWSTT-ready and not-ready participants for outcomes of both the SALL test and BWSTT trial (discussed below) added to the third section of the algorithm and proposed clinical decision-making tool, the assessment of volitional control. Four participants (P1,5,8,10) were recorded as unable to complete the SALL test due to no active range of hip and knee flexion either against gravity, or additionally for participant 8, against their tone (Table 7). The two participants (P2,3), who could attempt the SALL test but were clinically judged as not-ready for BWSTT both achieved less than 45 degrees of active flexion for both hip and knee joints. In comparison, the four participants (P4,6,7,9) clinically judged as ready for BWSTT all had greater than 45 degrees of active flexion for both hip and knee joints. Dorsiflexion results were inconsistent across the group. Assessment of volitional control was added as the third section of the algorithm and proposed clinical decision-making tool, with completion of the SALL test as the initial component. The results included are that people with less than 45 degrees of active flexion at both the hip and knee joints continue locomotor training on the Lokomat®, while people with more than 45 degrees of active flexion at both the hip and knee progress on to complete the BWSTT trial.

Assessment of Volitional Control - Body Weight Supported Treadmill Training Trial:

The four participants (P1,5,8,10) noted above as unable to attempt the SALL test were automatically judged as not-ready for BWSTT therapy, so did not attempt the BWSTT trial. Additionally, participant 2 was noted to use significant momentum of the trunk to achieve their small amount of hip and knee flexion in the SALL test, and as such was also excluded from the BWSTT trial and clinically judged as not-ready for BWSTT. Four (P4,6,7,9) of the five (P3,4,6,7,9) participants who completed the BWSTT trial were clinically judged as ready for BWSTT therapy. The kinematic, spatiotemporal parameters, and BWSTT settings of the five participants who completed the BWSTT trial are presented in Table 8.

Following observation of the BWSTT trial, participant 3 was clinically judged as not-ready for BWSTT. Following analysis of the video, participant 3 was found to have: a greater amount of BWS (>50%) than recommended in the literature with a larger stance knee flexion angle (>25 degrees); pelvic drift/rotation occurring for one third of steps; toe catch on more than 50% of steps; greater step length asymmetry (>7cm difference); no heel contact; a lower BWSTT speed (<1.0kph); inability to complete a satisfactory physiological gait pattern for one minute; and an inability to change these issues with verbal or physical facilitation by one therapist. Conversely, the four participants clinically judged as ready for BWSTT therapy were subsequently found to have:

less than 25 degrees knee flexion in stance with less than 50% BWS; less than 30% steps with pelvic drift; toe catch on less than 30% of steps; less than 7cm asymmetry between steps; heel contact on more than 75% of steps; and a BWSTT speed of at least 1.0kph where they were able to sustain their gait pattern for more than one minute and correct any issues, with either verbal or physical cueing from only one therapist. The need to review these factors in a BWSTT trial was added as the second component of the assessment of volitional control in the proposed algorithm and clinical decision-making tool, with the suggestion that where one therapist cannot assist with overcoming multiple issues, the patient continue with use of the Lokomat®.

Table 8: Body Weight Support Treadmill Trial Kinematics, Spatiotemporal and Device Data

		Participant				
Gait Cycle	**Measurement**	**P3**	**P4**	**P6**	**P7**	**P9**
	Clinical Decision for BWSTT	No	Yes	Yes	Yes	Yes
	BWSTT BWS Percent	52*	49	49	28	20
Mid Stance	Mid Stance Hip Flexion (degrees)	13	12	18	12	7
	Mid Stance Knee Flexion (degrees)	30*	14	23	23	1
Pelvis/Hip in Stance	Pelvic drift/rotation (% Yes of steps)	33*	100^	0	11	0
	Terminal Stance Hip Extension (degrees)	-6	-3	-17	-1	-1
Toe off/Toe catch	Toe off Hip Flexion (degrees)	11	9	30	9	18
	Toe off Knee Flexion (degrees)	49#	34	63	38	47
	Toe off Dorsiflexion (degrees)	-11	-21	-20	-9	-7
	Toe Catch Present (% Yes of steps)	56*	0	30^	0	0
Mid Swing	Mid Swing Hip Flexion (degrees)	18	13	33	21	22
	Mid Swing Knee Flexion (degrees)	54#	29	62	36	36
	Mid Swing Dorsiflexion (degrees)	-8	-14	-20	1	-10
Terminal Swing	Terminal Swing Hip Flexion (degrees)	28	18	33	29	26
	Terminal Swing Knee Extension (degrees)	-20	-9	-33	-25	-10
Step length	Difference affected to non-affected (cm)	7.9*	1.4	2.2	-4.1	-6.7
Foot contact	Foot contact Hip Flexion (degrees)	20	19	28	24	20
	Foot contact Knee Extension (degrees)	-19	-11	-32	-20	-10
	Heel strike (% Yes of frames)	0*	83	0	78	100
	Midfoot strike (% Yes of frames)	100*	17	0	22	0
	Forefoot strike (% Yes of frames)	0	0	100@	0	0
Limb Speed	Video calculated limb speed (km/h)	1.1*	1.6	0.8	1.8	2.1
	Actual BWSTT device speed (km/h)	0.7*	1.0	0.6@	1.0	1.6

*Items participant 3 judged as not-ready for BWSTT. #Participant: 3 increased knee flexion at toe off and mid-swing from delayed/poor toe off and passive range created from being on tip-toe as toe catching. ^items controlled by verbal or physical facilitation from one therapist. @Participant 6: usual gait pattern forefoot strike and slower speed.

Figure 3a) Clinical Decision Making Algorithm and Study Participants Flow.

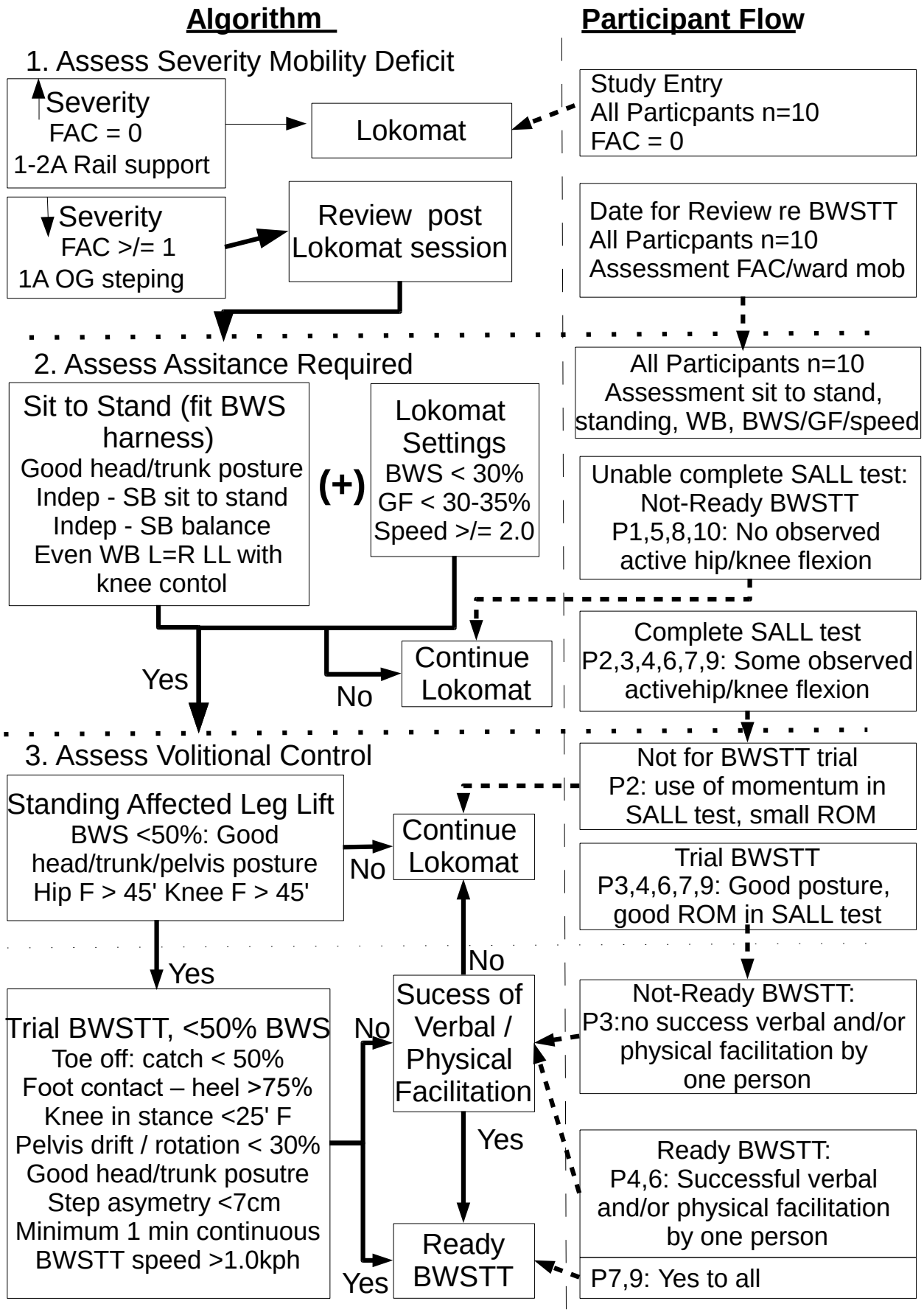
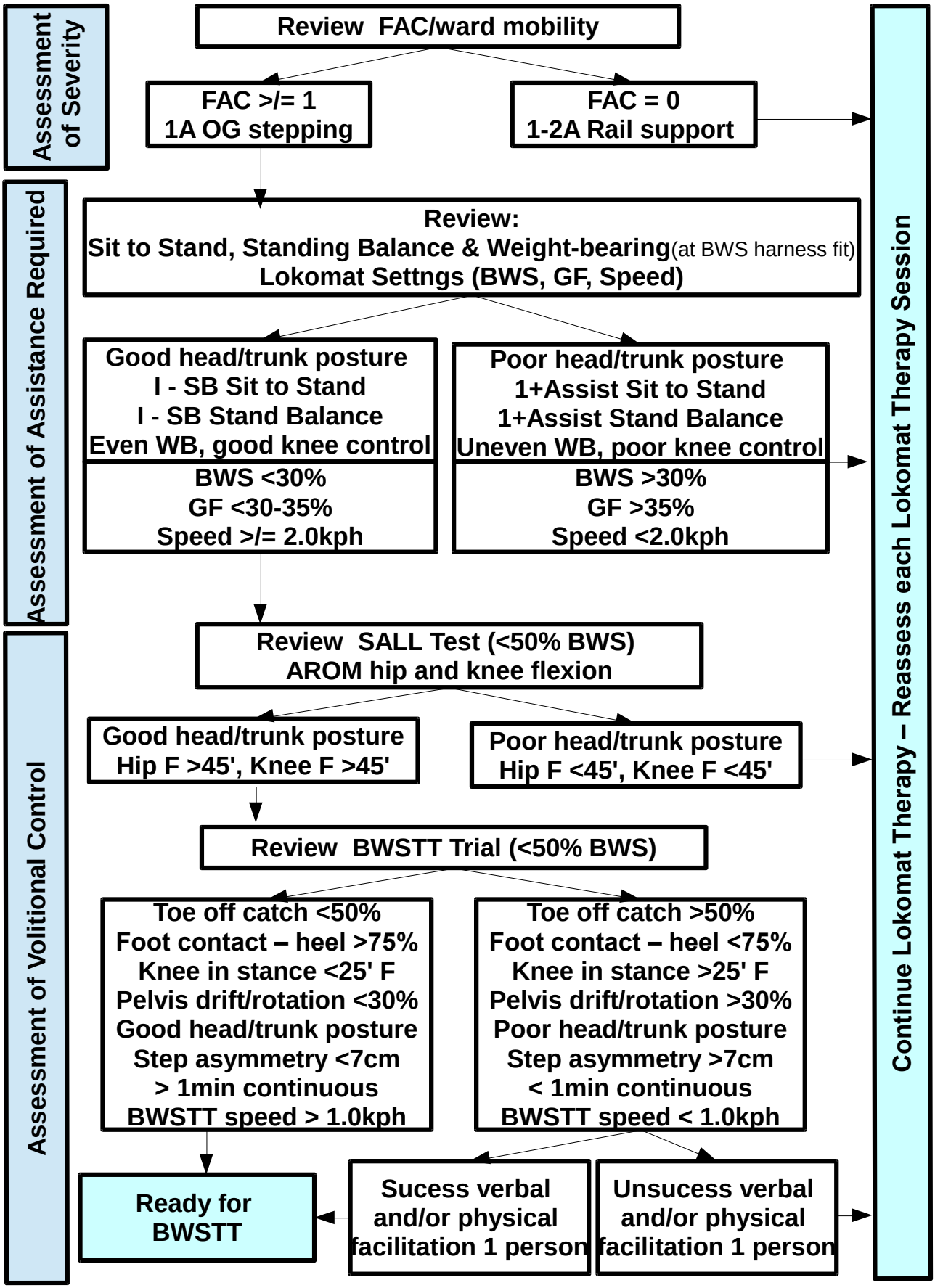


Figure 3b) Clinical Decision Tool



3.5 Discussion:

The aim of this study was to develop an algorithm that could inform a proposed clinical decision-making tool regarding readiness for BWSTT therapy in subacute stroke, based on outcome measures and concepts from previous literature relating to severity of impairment, amount of assistance required, and amount of volitional control. The study results suggest that participants ready to complete BWSTT therapy have: (1) reduced severity noted by a FAC of 1, having progressed towards some overground mobility with assistance from one therapist; (2) less need for assistance observed as no physical assistance with sit to stand or balance and even weight-bearing in standing, and objectively measured as Lokomat® BWS less than 30%, GF less than 30-35%, and speed above 2.0kph; (3) greater volitional control demonstrated by standing active hip and knee flexion greater than 45 degrees each, good knee extension in the stance phase of gait (<25 degrees flexion) with less than the recommended 50% BWS (Hesse, 2008), good hip and pelvis control in terminal stance with less than 30% of steps having pelvic drift or excess rotation, effective toe off with catching less than 50% of the time, heel strike on more than 75% of steps, symmetry of steps (<7cm difference), increased speed of movement in BWSTT with the ability to complete BWSTT at 1.0kph or more for a minimum of one minute, and less need for (or successful use of) verbal cue correction or physical facilitation from only one therapist while completing BWSTT. These criteria were incorporated into the presented algorithm and proposed clinical decision-making tool under the sections of severity, assessment of assistance required, and assessment of volitional control as the previously established broad concepts within the literature regarding progression from robotics to BWSTT (Backus & Tefertiller, 2008; Hornby et al., 2010; Hornby et al., 2005).

Of the ten participants in the current study, the four clinically judged following the SALL test and BWSTT trial as ready for BWSTT therapy were all completing overground locomotor training, mostly with the assistance of one therapist, and hence the majority of BWSTT-ready participants received a FAC of 1 at the point of review. In comparison, the six not-BWSTT ready participants typically required assistance from two therapists, and commonly also used the rail for support during therapy, so mostly received a FAC of 0 at the time of review. The recent Cochrane review associates a FAC below 4 as the more severely affected mobility-dependent patients post-stroke (Mehrholz et al., 2017b), To be consistent with this, FAC is aligned with the concept of severity of mobility impairment in the proposed algorithm and clinical decision-making tool. This is in contrast to the use of a specific motor severity scale, such as the ASIA scale used by Backus and Tefertiller (2008) for spinal cord injury, but is similar to the use of FIM motor by Backus and Tefertiller (2008) and Hornby et al. (2005). Furthermore, use of FAC may be supported by the 2005 study by Hornby and colleagues, which recommended general mobility status be considered regarding readiness for BWSTT rather than any specific motor outcome measure. Within the proposed algorithm and

clinical decision-making tool, severity is divided into those with a FAC of 0 being suggested as suitable to continue on the Lokomat® and those with a FAC of 1 to be further considered for BWSTT through use of the rest of the tool. While lower than the recommendation in the Cochrane review of robotics for people with a FAC below 4 (Mehrholz et al., 2017b), the need to review participants with a FAC of 1 regarding readiness for BWSTT aligns with the fact that most contention of which modality to use, or when to transition from the Lokomat® to BWSTT, relates to patients who have some lower limb motor ability which would exist with a FAC of 1 (Backus & Tefertiller, 2008; Hornby et al., 2005).

With regards to the assessment of the amount of assistance required, the second concept in the literature, in the current study the BWSTT-ready participants were observed to have more independence in sit to stand and standing balance with even weight-bearing while fitting the BWS harness. They were also noted to have more advanced Lokomat® settings with a BWS less than 30%, GF less than 30-35%, and speed at or above 2.0kph. Conversely, the participants not-ready for BWSTT were observed to need more support with sit to stand and balance, having uneven weight bearing, and higher BWS and GF, and lower speed. Assessment of the assistance required for trunk support, standing posture, and leg support in stance and movement in swing are included in the previous work on progression of therapy and modality choice in SCI (Backus & Tefertiller, 2008; Behrman et al., 2005; Hornby et al., 2005). We therefore suggest to include trunk/standing posture and knee control in the proposed decision-making tool, with sit to stand, standing and weight-bearing assessed as outcome measures. Furthermore, BWS and speed were similarly considered as indicators for progression from robotics to BWSTT by Hornby et al. (2005), although GF was not discussed. Assessment of assistance required, as the second section of the proposed algorithm and clinical decision-making tool, therefore includes a) clinical observation of the assistance required to complete the functional task of sit to stand, stand with balance while weight bearing evenly for fitting the BWS harness and, b) the assistance provided through the Lokomat® settings. The algorithm and proposed clinical decision-making tool suggest that patients with independence in sit to stand, who stand independently with good posture and even weight bearing, and have Lokomat® settings of BWS less than 30%, GF less than 30-35%, and speed at or greater than 2.0kph, have an assessment of their volitional control as the third section of the algorithm and proposed clinical decision-making tool. Conversely, patients needing assistance from one person for sit to stand, to stand with balance, or have uneven weight-bearing, and Lokomat® settings of BWS greater than 30%, GF greater than 35%, and speed lower than 2.0kph, are suggested to continue using the Lokomat® for locomotor therapy.

The current study results demonstrated that participants clinically judged as ready for BWSTT had greater than 45 degrees of both active hip and knee flexion when completing the SALL test, whereas the participants who completed the SALL test but were not-ready for BWSTT had less active hip and knee flexion. Compared to the participants who were considered ready for BWSTT, participant 3, who was clinically judged as not-ready for BWSTT, was found to have: a BWS greater than the recommended 50% (Hesse, 2008) with ongoing knee flexion in stance averaging 30 degrees; pelvic drift for a third of steps; toe catch at toe-off for over 50% of steps; decreased symmetry of step lengths (>7cm difference); no heel strike; a slower speed of limb movement and BWSTT speed; and an inability to sustain a physiological gait pattern for even one minute. Compared to participants in the BWSTT-ready group that also required some facilitation, the issues for participant 3 could not be assisted by verbal cueing or physical facilitation from one person, a component of assessment which is also included in the work by Behrman et al. (2005). The lack of knee control in stance and toe catch is noted by Hornby et al. (2005) to also be important for a good physiological gait in robotic therapy, such that potentially these are two key factors warranting future exploration.

Assessment of volitional control as the third broad concept presented in literature has previously incorporated both static and dynamic assessments as per the work by Behrman et al. (2005) for SCI. As such, the third section of the algorithm and proposed clinical decision-making tool is assessment of volitional control, initially using the more static SALL test, followed by a dynamic trial of BWSTT. The algorithm and proposed clinical decision-making tool suggest that greater than 45 degrees of active hip and knee flexion are required in the SALL test in order to be likely of being ready for BWSTT therapy. A number of kinematic and spatiotemporal factors were identified as potentially relevant clinical differences between the one participant who completed the BWSTT trial, but was clinically judged as not-ready for BWSTT, to the four other participants judged as ready for BWSTT. The key clinical indicators of a successful BWSTT trial, as described above, were also then added into section three, assessment of volitional control, of the algorithm and proposed clinical decision-making tool, including the use of verbal and physical facilitation from one person as acceptable to be considered ready for BWSTT therapy.

The stages of the proposed algorithm and clinical decision-making tool were intended to be applied in the order of severity, assessment of assistance required, and assessment of volitional control, although it is important to note that the criteria presented are not mutually exclusive, a consideration supported by others (Backus & Tefertiller, 2008; Hornby et al., 2005). In addition, a patient can be progressed through as many stages of the clinical decision-making tool as required until a clear decision is made, with the algorithm and clinical decision tool demonstrating the likely

outcome at each level with regard to being BWSTT ready. Besides aiding clinical decision-making, further justification of the need for, and potential use of the algorithm and clinical decision tool developed, relates to the ongoing need for further research comparing the efficacy of the two modalities, necessitating a clinical decision point of being ready for BWSTT. To enable this research further validation of the proposed clinical decision-making tool and its associated cut off points is required.

Limitations of the current study include the small sample size thus limiting statistical analysis, the use of observational data, a lack of follow-up for participants post discharge from inpatient subacute rehabilitation, and bias of the principle investigator being the treating therapist on the Lokomat® and data collector (non-blinding). A repeated inter-therapist process using the clinical decision-making tool in a larger number of patients with stroke would be required to further validate or refine sections of the proposed algorithm and tool. Other additional benefits for future research would include adding an assessment of standing affected knee control, potentially using a marching action instead of the SALL, increased participant number, and delineation of who to complete a BWSTT trial with through collection of more data. Finally, integration of the use of path control in comparison of Lokomat® settings in future research is warranted as is exploration of key decision points such as toe off and knee control.

3.6 Conclusion:

An algorithm is presented to guide progression of locomotor therapy, or choice of modality, between the Lokomat® and BWSTT therapy in subacute stroke, and has been translated into a proposed clinical decision-making tool.. Patients with a FAC of 0 are suggested as needing to continue on the Lokomat® while those with a FAC of 1 are reviewed using the proposed tool for readiness for BWSTT therapy. Patients who are more independent with sit to stand, stand without therapist support for balance, with even weight bearing, and have Lokomat® settings of BWS<30%, GF<30-35%, and speed >/=2.0kph, can be considered for review of volitional limb control. Patients with standing active hip and knee flexion above 45 degrees each warrant a trial of BWSTT, whereby those clinically ready for BWSTT are likely to have less than 25 degrees stance knee flexion with BWS <50%, toe off without catching less than 50% of steps, hip and pelvic drift less than 30% of steps, less than 7cm asymmetry of steps, heel-strike >75% of steps, can manage to complete BWSTT at 1.0kph or more for a minimum of one minute, and if verbal or physical facilitation is required it can be provided by only one therapist. Further validation on a larger sample size allowing statistical analysis is required for the current proposed tool.

4. DISCUSSION

Due to previous literature in stroke suggesting low intensity CV training on the Lokomat®, without specific previous review of the APF activities, and a gap in literature regarding transition to BWSTT in stroke, the aims of the current study were:

1. To determine: Can the Lokomat®, with use of the APF activities, be used to complete sustained moderate intensity CV exercise in patients with subacute stroke?
    a. Can a moderate intensity level of CV exercise be achieved using the APF activities?
    b. Is there a difference in the intensity achieved between different APF activities used?
    c. Can moderate intensity CV exercise be sustained for a minimum 10-minute duration?
    d. Do clinical changes in Lokomat® device settings influence the CV workload achieved?
    e. Does participant motivation and enjoyment influence CV workload outcomes?
    f. Can the BORG CR-10 scale be used clinically to ascertain intensity levels while completing APF activities on the Lokomat®?
2. To develop an algorithm and propose a clinical decision-making tool guiding progression from the Lokomat® to BWSTT in subacute stroke, based on criteria supporting the concepts of patient severity, amount of assistance required, and degree of volitional control.

4.1 Thesis Key Findings

Achieving CV exercise with intensity and duration in line with the National Stroke Guidelines in subacute stroke rehabilitation is difficult, particularly in mobility-dependent patients post-stroke. In the current study, using the Faster, Gabarello 2, and Graph APF activities of the Lokomat®, a moderate intensity of CV exercise was achieved as demonstrated by: a mean (SD) VO_2 of 8.0ml/kg/min (3.8), approximated to 52% VO_2max; MET values greater than 3; and BORG CR-10 scores between 3 and 5 for both breathing and leg perceived effort. The moderate intensity of CV exercise was sustained for 15 minutes and was not influenced by which APF activity was completed, or by a reduction in the Lokomat® BWS and GF. Most importantly regarding the CR-10 scale, the subjective BORG scores aligned clinically with the objective moderate intensity level achieved. However, a statistically poor correlation of the BORG scores to oxygen consumption was found (see Appendix 3), noted also by statistical differences for BORG scores, but not VO_2, in the type of APF activity completed, as well as the order of activity completion. While motivation was consistent for each APF activity completed and over all study sessions, enjoyment was found to be greater for the Graph APF.

Knowledge of indicators regarding readiness to transition to BWSTT in stroke are limited (Manickavasagam et al., 2015). An early transition may be warranted to maintain or progress CV exercise intensity, as well as enable high-dosage repetitive functional task-specific practice with inherent step-variability and less risk of passive over-assistance. In the current study, several differences were noted between participants clinically judged ready for BWSTT as compared to participants clinically judged not-ready for BWSTT. An algorithm and clinical decision-making tool were proposed guiding choice of modality for locomotor therapy, and transition from the Lokomat® to BWSTT, in subacute stroke. The key decision points of the algorithm and clinical decision tool include: differentiation between a FAC of 0 and a FAC of 1; whether assistance is required or not from one or more therapists in completing sit to stand, standing balance and evenness of weight-bearing during fit of the BWS harness; the assistance provided by the Lokomat® settings with a BWS of 30%, GF of 30-35%, and speed of 2.0kph as the relevant settings; achievement or not of 45 degrees of active range at both hip and knee flexion in standing with less than 50% BWS; and whether only one person is required to assist multi-components of a physiological gait pattern in BWSTT completed at less than 50% BWS.

4.2 Participants

Ten participants meeting eligibility (inclusion/exclusion) criteria provided consent for inclusion into the research study between September 2017 and January 2018. Nine participants completed all six data collection sessions regarding CV exercise on the Lokomat®, however one participant only completed the initial two sessions before having knee pain that prevented ongoing use of the Lokomat®. Concurrently, this participant's gait improved to proceed onto BWSTT when therapy sessions recommenced, so remained included in the analysis of transition to BWSTT without further use of the Lokomat®. Due to the randomisation of the APF activities, it was deemed appropriate to keep the data that was collected on this participant relating to CV workload with the APF activities, rather than withdraw the participant from the study and recruit a new substitute participant.

Overall, participant demographics were representative of a typical group of adult mobility-dependent patients with stroke in the subacute phase of inpatient rehabilitation accessing the Lokomat® robotic. The ratio of male to female participants did make results less applicable to female patients with only two of the 10 participants in the current study being female, and one of the two was the participant described above who was only able to complete two of the six CV exercise study sessions. Although the Lokomat® can be used by patients with a wide range of cognitive ability, all participants in the current study were able to consciously increase active participation, engage with the APF activities, and follow instructions for BWSTT, as compared

potentially to other patients with less cognition. With the exceptions of cognitive capacity and gender, the age, ratio of ischaemic to haemorrhagic stroke, and left and right body side affected, is well represented in the current study relative to the stroke population. At study inclusion, all participants had the same FAC of 0, demonstrating they were the most immobile participants, unable to easily perform walking based CV exercise without robotic support and warranting a trial of Lokomat® therapy (Mehrholz et al., 2017b).

4.3 Augmented Performance Feedback Activities of the Lokomat® and Cardiovascular Workload

The current study demonstrated that using the APF activities of the Lokomat®, mobility-dependent adult patients with stroke in subacute rehabilitation can achieve sustained moderate intensity CV exercise that is in line with the recommended guidelines, irrespective of the particular APF activity completed. In the current study, for the objective measures of VO_2 and MET, the participants achieved a pooled mean (SD) active VO_2 of 8.0ml/kg/min (3.8) and MET of 3.1 (1.3) while completing the included APF activities on the Lokomat®. A comparison of the active VO_2 achieved to VO_2max is required in order to determine the intensity level attained when using VO_2 measures. The previously defined parameters of moderate intensity exercise are 40-60% VO_2reserve, or where using MET: 3-6MET, or alternatively 3-4 points on the BORG CR-10 scale (American College of Sports Medicine, 2014; Norton, 2010; Riebe et al., 2015; Wittink et al., 2017). Completion of a CPET to determine VO_2max was not feasible in the current study due to safety and resource issues, as well as the study confined to being an observation of usual clinical practice. Therefore, similar to methodology of a previous study (Han et al., 2016) the results achieved by current study participants were compared to a similar cohort completing a CPET to VO_2max on the Lokomat®, given that the choice of CPET modality is known to influence outcomes (Stoller et al., 2014a; van de Port et al., 2015).

Stoller and colleagues (2014a) completed a CPET on the Lokomat®, with 14 participants who were less than 20 weeks post-stroke and had a FAC 0-2, and found a VO_2 peak of 15.5 +/- 4.9 ml/kg/min. Within this study, it was considered that adequate CPET protocols were used via a previously tested methodology, with 57% of study participants meeting one of three criteria for a maximal test (Stoller et al., 2014a). All participants were also noted as being limited by generalised and/or leg fatigue in reaching any further maximal effort (Stoller et al., 2014a). Comparing the current study participants active VO_2 of 8.0 +/- 3.8 ml/kg/min to the VO_2 peak found by Stoller et al. (2014) of 15.5 +/- 4.9 ml/kg/min demonstrates that current study participants achieved an average CV exercise intensity of 52% VO_2max, which classifies as moderate intensity CV exercise. This is

similar to the CV intensity of 51.6% +/- 20.5% VO_2max reported in the study by Stoller and colleagues (2014a), and to the 50-56% VO_2max suggested by Han et al. (2016).

The VO_2 peak of 15.5 +/- 4.9 ml/kg/min in mobility-dependent subacute stroke patients completing a CPET on the Lokomat®, presented by Stoller et al. (2014), is comparable to the peak VO_2 achieved for similar cohorts (mobility-dependent patients with subacute stroke) completing a CPET on other devices. For example, results for mobility-dependent patients with subacute stroke on bike ergometry include peak VO_2 results of 15.7 +/- 5.6 and 14.1 +/- 4.8 ml/kg/min in a study by Chang et al. (2012), and 14.04 +/- 3.33 and 14.98 +/- 4.26 ml/kg/min in a study by Han et al. (2016). More mobile subacute patients with stroke on a recumbent stepper achieved a peak VO_2 of 15.8 ml/kg/min (Billinger et al., 2012b). In a systematic review by van de Port et al. (2015) exploring CPET completed in stroke, the maximum workload in subacute stroke was demonstrated to fall between a VO_2peak of 8 and 20 ml/kg/min regardless of testing device, testing protocol, or functional ability of the participants. Similarly, Smith et al. (2012), in their systematic review of CV fitness in both subacute and chronic stroke, reported a range of VO_2 peak between 8 and 22 ml/kg/min, regardless of participant mobility level, and using all available modalities for CPET. Translating the results from Smith et al. (2012) to the current study suggests that the current study participants were exercising from near moderate intensity (36%) to maximal (100%) of their capacity. Finally, Marsden et al. (2013), in their review of 28 studies relating to efficacy of CV exercise in stroke, found that 24 of the 28 included studies reported the mean VO_2peak post-stroke to be below the recommended 18ml/kg/min required for independence. When translating these findings to the current study, i.e. interpreting 18ml/kg/min as the maximal VO_2 achievable post-stroke, once more this implies that participants in the current study would have been exercising at a moderate intensity (44%).

Current study participants achieved a MET of 3.1 +/- 1.3, whereby a MET of 3 to 6 constitutes moderate intensity CV exercise (American College of Sports Medicine, 2014; Norton, 2010). This further supports the assertion that study participants achieved moderate intensity CV exercise while completing the APF activities of the Lokomat®. While MET is often reported as an estimation, whereby rest is the equivalent of 1 MET and approximated to a VO_2 of 3.5ml/kg/min, the MET reported in the current study was calculated by the more accurate method of dividing active VO_2 by resting VO_2 giving a more precise and individualised result. Furthermore, current study participants had an overall self-perceived BORG score of 3.5 +/- 1.7 for BORG-D and 4.8 +/- 1.7 for BORG-L, where clinically a range of 3 to 4 on the BORG CR-10 scale is considered moderate intensity (American College of Sports Medicine, 2014; Billinger et al., 2014; Borg & Kaijser, 2006; Ivey et al.,

2005; Norton, 2010; Zamunér et al., 2011). This further strengthens the assumption that moderate intensity of CV exercise was achieved.

In contrast, a recent systematic review by Lefeber et al. (2016), evaluating CV exercise on a range of robotic devices concluded that intensity of CV exercise on robotics is generally inadequate to meet guidelines for moderate intensity (Lefeber et al., 2016). The authors of this systematic review do, however, acknowledge that the outcomes of CV workload may depend on specifics of device type, device settings, and participant cohort. It should be noted that there was a large degree of heterogeneity between included studies, with only one of the included studies involving patients with stroke on the Lokomat® (van Nunen et al., 2012). The study by van Nunen et al. (2012), comparing intensity in overground and Lokomat® walking in healthy and stroke participants, states that the participants with stroke on the Lokomat® did not meet even 30% of HRR. However, HRR was calculated using an estimated formula, and HR has previously been noted as not being reliable in patients with CV compromise such as stroke, or while on robotics (David et al., 2006; Krewer et al., 2007; Smith et al., 2012; Stookey et al., 2013). Furthermore, as no CPET was completed on the participants with stroke, the potentially more accurate VO_2 results could not be calculated into intensity by comparing within participant to a VO_2max test. Amongst these and other limitations, including the fact that extrapolations were made between healthy and stroke participants regarding workload on the Lokomat®, the study by van Nunan et al. (2012) lacks detail regarding the device settings used for stroke participants, and the use of the Lokomat's® APF activities, or any other form of feedback or motivation that could increase active participation (Banz et al., 2008; Deutsch et al., 2012; Koenig et al., 2011). Participants with stroke in the study by van Nunen et al. (2012) were noted to have a mean VO_2 of 9.3 +/- 1.6 ml/kg/min while active on the Lokomat®, but with unknown device settings. This is a higher VO_2 than achieved in the current study, consistent with more mobile stroke participants, such that it is likely a moderate intensity was in fact reached, a suggestion also supported by Han et al. (2016).

The current study demonstrated no significant differences in the CV intensity achieved between the three APF activities, measured objectively with VO_2 and MET, and subjectively with BORG-L. This either suggests that the level of CV work achieved while on the Lokomat® is determined by other factors, or that each of the tested APF activities has a similar ability to attain the same CV workload. Participants did perceive a higher work of breathing (BORG-D) in the Faster APF activity as compared to the Gabarello 2 APF activity, but not as compared to the Graph activity. This could be explained by the different visual stimulus of the interval-based racing environment of the Faster APF creating a greater perceived level of work. This is supported by the work of Riedo and Hunt (2017), where it is discussed that a visual stimulus can influence HR responses which in turn would

influence perceived effort (Borg, 1982). As the objective measures of CV workload intensity did not vary between the different APF activities completed, the choice of APF activity to be completed in a clinical therapy session can potentially be based on therapist recommendation, patient goals, purpose of the APF activity, or patient preference.

Along with the level of intensity achieved, part of the FITT criteria to achieve CV exercise and be in line with recommended guidelines, as described by Ammann et al. (2014), is sustained moderate intensity over a minimum 10 minute duration. In the current study, no difference was found in the objective measures for CV exercise intensity, as measured by VO_2 and MET, between the APF activities completed in the first, second and third five minute blocks. This demonstrates that participants were able to maintain the same CV intensity over the full 15 minutes. Subjectively, self-reported workload, as measured with BORG-D and BORG-L, whilst still in a moderate intensity range, was lower for the first completed APF activity, and then maintained for the second and third completed APF activity. The lower subjective/perceived BORG-D and BORG-L scores for the first completed APF activity was incongruent to the results of the objective outcomes of VO_2 and MET, but is consistent with patterns of greater perceived effort of breathing and leg work in the latter half of training (Eston, 2012). Despite the statistical difference in BORG scores from the first to second, and first to third completed APF activities, clinically this difference was minimal, with on average only a 0.5 point change in score on the BORG CR-10 scale. The fact that the affected-leg effort was demonstrated by current study participants as sustained for the full 15 minutes is important, given the concerns raised previously that participants completing a CPET on the Lokomat® may only be using their unaffected side to increase workload (Stoller et al., 2014a; Stoller et al., 2015). This concern prompted the current researcher to add within the current study the specific question of “how hard is your affected leg working”, using the BORG-L scale, enabling subjective monitoring of perceived use of the affected limb. Furthermore, the APF biofeedback settings were maintained on a bilateral setting for feedback purposes, and to encourage use of the affected side.

In summary, participants in the current study demonstrated a sustained moderate intensity CV workload across 15 minutes without significant metabolic or subjective fatigue, and with no reduction in perceived leg effort. This is an important finding since in previous studies stroke participants have demonstrated an inability to maintain walking overground for long enough to meet the duration criteria for CV exercise (David et al., 2006; van Nunen et al., 2012). Furthermore, previous concerns were raised as to whether a minimum 10 minutes of sustained moderate intensity exercise could be achieved by mobility-dependent patients on the Lokomat® (Stoller et al., 2014a; Stoller et al., 2013; Stoller et al., 2014b). Patients with stroke themselves have reported endurance post-stroke as being important for successful community ambulation

(Barclay et al., 2015), suggesting a need to ensure this element is included in locomotor therapy. Han et al. (2016) and Lefeber et al. (2016) theoretically discuss the likely benefit of robotic therapy for sustained duration of exercise, with Krewer et al. (2007) objectively demonstrating that robotic training allowed a longer duration of activity than did BWSTT in stroke participants. As such, the use of technology such as robotics, by providing a certain level of support, may enable patients to meet the duration criterion of the FITT principles of CV exercise, and as evidenced in the current study, moderate intensity can be achieved.

4.3.1 Lokomat® Settings and Cardiovascular Workload

Lokomat® speed, which in the current study was the participant's self-selected maximal, did not vary significantly over the six study sessions. However, as per usual clinical practice, Lokomat® BWS and GF in the current study were purposely decreased between the six study sessions, leading to a statistically significant reduction of BWS and GF. The reduction in BWS and GF did not, however, equate to a higher CV workload either objectively, as measured with VO_2 and MET, or subjectively, as measured by BORG-D and BORG-L. This is in contrast to previous literature suggesting that particularly a lower BWS, and potentially to a lesser degree, a lower GF, would likely result in a higher CV workload (Krewer et al., 2007; Krishnan et al., 2013a; Lefeber et al., 2016; Schindelholz et al., 2014; Stoller et al., 2013; Van Kammen et al., 2014; van Nunen et al., 2012). However, the impact of the Lokomat® settings on CV workload remains an area for further investigation as varying and inconsistent results exist (Lefeber et al., 2016). Furthermore, clinically over the six sessions in the current study, the BWS only decreased on average from 40% to 30% and GF from 55% to 40%. A more detailed review of the Lokomat® settings used in the literature presented above suggests a greater amount of change in BWS or GF than was provided in the current study may be required to elicit an increased CV workload. For example, one previous study (David et al., 2006) only noted a higher CV workload at a BWS of 0% and other studies included a BWS and GF as low as 0% and 20% in their research (David et al., 2006; Delussu et al., 2014; van Nunen et al., 2012). A consideration for further research to assist in standardising results between studies would be to present GF relative to participant weight, leg mass, or leg muscle ability, similar to how BWS is represented as a percentage of participant weight, whereas currently GF is usually presented in the literature as a percentage of the Lokomat's® total capacity of force provision.

Another possible explanation for why no change was observed in the objective or subjective CV workload measures over the six sessions, despite a statistically significant change in the Lokomat® settings, is that participants' CV fitness may have improved over the six study sessions, which were completed within eight to twelve days. This would be consistent with a finding from Chang et

al. (2012), who found a training effect after only two weeks of exercise on the Lokomat®. This possibility may have led to the same objective and subjective CV intensity being achieved at more challenging BWS and GF settings over each of the six sessions of the current study. A lower active VO_2 result may have otherwise occurred over time in the current study if Lokomat® settings had remained constant over the six sessions while participants' CV fitness concurrently improved. This proposal is consistent with a similar finding by Macko et al. (2001), where a 15% lower aerobic capacity resulted at follow-up CEPT testing completed after a CV training phase, where the relative workload demand on the treadmill was kept the same for the pre and post CPET tests. This highlights the need to progressively challenge patients with lower BWS and GF settings to ensure a moderate intensity level of CV exercise is maintained.

4.3.2 Motivation and Enjoyment During Augmented Performance Feedback Activities of the Lokomat®

Besides encouraging and monitoring sustained use of the affected leg, one of the primary purposes of the virtual reality based APF activities of the Lokomat® is to provide motivation and enjoyment through real-time interactive feedback. In the current study, there was no difference in motivation scores between the three APF activities completed, over the duration of a single study session, or over the course of the six study sessions. Similarly, enjoyment scores did not differ over the duration of a single study session or over the course of the six study sessions, however, enjoyment scores were higher for the Graph APF activity as compared to either Faster or Gabarello 2. A variance in patient opinion toward different activities and feedback options on the Lokomat® was also reported by Lunenburger et al. (2004) and Banz et al. (2008). Previous studies have used different forms of feedback in an attempt to engage participants and influence CV workload, such as HR guided graphs, line graphs representing mechanical torque, the BORG scale, and virtual reality activities (Bae et al., 2016; Koenig et al., 2011; Schindelholz et al., 2014; Stoller et al., 2014a; Stoller et al., 2015; Stoller et al., 2013; Stoller et al., 2014b). Bae et al. (2016) has provided evidence of a preference towards the use of HR guided targeted feedback compared to use of the BORG scale to achieve higher CV workloads. However, it is also known HR may not be an appropriate measure of intensity in this clinical group or on robotic devices (David et al., 2006; Eng et al., 2004; Krewer et al., 2007; Smith et al., 2012; Stookey et al., 2013). Schindelholz and colleagues (2014), following on from the CPET series of work by Stoller and colleagues (2013, 2014a, 2014b, 2015), developed specific software based on line graphs comparing desired to actual mechanical torque designed to guide training intensity, and had reasonable results regarding an influence on workload levels. Koenig et al. (2011) believe factors intrinsic to individual patients might more so drive decision-making regarding the type of feedback used, noting all options of HR, torque graphs, and virtual reality activities as being useful with results dependent upon the individual patient. The Graph APF, most enjoyed by participants in the current study,

most closely relates to the mechanical torque concepts used in the work by Stoller, Schindelholz, Koenig and their respective colleagues, or the WIT concept used by Koenig et al. (2011). Given there was no variance in objective outcomes for VO_2 or MET in the current study, therapist choice of APF activity according to desired therapy outcomes, and patient preference of preferred activity such as with the Graph activity, would seem appropriate.

4.4 BORG as a Measure of Cardiovascular Intensity in Lokomat® Gait Training

In most clinical settings, metabolic testing cannot feasibly be completed on all patients accessing the Lokomat®, hence further investigation into the use of a subjective scale such as the BORG is important. In the current study, weak statistical correlations were found between VO_2 and both BORG-D and BORG-L (see Appendix 3), whereby some participants with lower VO_2 results perceived themselves as working harder according to either of the BORG scores. As VO_2 is related to the use of muscle mass, the participants in the current study with low VO_2 but high BORG scores may have been working at a higher self-perceived rate, and their maximum possible physical ability, but were simply unable to generate a greater VO_2 due to lower available muscle recruitment. As such, these participants may essentially be unavoidably relying on the unaffected side to physiologically generate the VO_2 level as suggested by Stoller et al. (2014, 2015). Whilst all participants in the current study were the most mobility-dependent, and hence had a FAC score of 0 on study enrolment, there was still great variability between participants regarding the degree of leg muscle recruitment observed while preparing participants during set-up of the Lokomat®. This may have influenced the variability in achievable VO_2, and therefore the poor correlation with BORG scores. Sensory ability of participants was also not analysed in the current study, which may influence perceived scores relating to affected-leg effort. Furthermore, the BORG CR-10 scale has a very limited number of data points, which occur within a very small range of the overall scale. It would, therefore, be expected that correlation analysis may not be optimal as the magnitude of change at each point on the BORG CR-10 scale is not going to be sensitive enough to match with VO_2 changes. Investigation into the use of the 100-point version of the BORG scale, the centiMax scale, may be warranted, with a likely need for a greater number of participants as well.

Further to the above, participants scored higher on the BORG-D scale while completing the Faster APF activity, compared to the Gabarello 2 activity, without any difference in objective measures of VO_2 or MET between these two APF activities. This further highlights the need to be cautious when using the BORG scale on the Lokomat®. This result is consistent with other studies incorporating BORG and the Lokomat®, where higher workloads have been achieved using HRR targets than could be achieved with the BORG scale under the same test conditions (Bae et al., 2016), further adding to the question regarding use of the BORG scale on the Lokomat®. Furthermore, as

reported previously, other studies investigated that visual stimulus alone can affect HR (Riedo & Hunt, 2017) which relates to perception of effort (Borg, 1982). This adds to the evidence that both HR and the BORG scale may not be the most accurate measures of intensity while completing the visually stimulating APF activities on the Lokomat®. In stroke patients not on the Lokomat®, Sage et al. (2013) demonstrated validity of the BORG CR-10 scale during moderate intensity exercise, however this was not true at higher intensities. Adding to the debate regarding the use of BORG in stroke, Wu, Dong, Hu, Li, and Shi (2015) found the original BORG scale did not correlate to oxygen uptake for patients with stroke completing simple functional rehabilitation activities such as sit to stand, stair climbing, or a 60m walk. As such, the use of the BORG scale in patients with stroke, including while on the Lokomat®, needs ongoing investigation.

Despite the weak statistical correlation of the BORG scale with VO_2 in the current study, clinically, participants in the current study, as a pooled average, scored themselves between a 3 and 5 on the BORG CR-10 scale. Most importantly, this matches the desired target range and objective measures achieved by participants for moderate intensity CV exercise. Consistent with another study by Zamunér et al. (2011) investigating the BORG RPE CR-10 scale relative to the anaerobic threshold, the BORG-L score in the current study is greater than the BORG-D score, raising the question of which should be considered more relevant. This finding is also consistent with studies noting affected-leg fatigue rather than breathing to be the limiting factor leading to the cessation of the CPET on the Lokomat® in stroke (Stoller et al., 2014a; Stoller et al., 2015). Finally, participants in the current study demonstrated that while completing any of the included APF activities of the Lokomat®, with device settings at the lowest clinically achievable BWS and GF, a moderate intensity CV workload was achieved, regardless of the BORG score, and without targeting a particular BORG score, HR, or mechanical workload. This raises the question of, regardless of the desire to use a subjective rating to assist in either targeting or monitoring CV workload, whether any particular measure is specifically required. Alternatively, ensuring the lowest appropriate BWS and GF, and highest possible speed are used and progressed consistently in therapy sessions, may be adequate to assume a moderate intensity of CV exercise is achieved.

4.5 Transition from the Lokomat® to Body-weight Supported Treadmill Training

The study results suggest that, compared to participants clinically judged as not-ready for BWSTT, participants who were clinically judged as ready to complete BWSTT had: a) progressed towards some overground mobility with less support thus receiving a FAC of 1; b) minimal or no assistance with sit to stand and standing balance, with equal weight bearing; c) Lokomat® BWS less than 30%, GF less than 30-35%, and speed at or above 2.0kph; d) active hip and knee flexion of more than 45 degrees each of the affected leg in standing; e) good knee extension in stance (<25

degrees) with less than 50% BWS, good hip and pelvis control in terminal stance with pelvic drift less than 30% of the time, effective toe-off with toe catch occurring in less than 50% of steps taken, heel strike occurring in more than 75% of steps taken, greater symmetry of step length (<7cm difference), increased speed of movement (BWSTT >1.0kph), and less need for, or successful use of, verbal cue correction or physical facilitation from only one therapist while completing BWSTT. These outcomes, noted from the comparison between participants not-ready and participants ready for BWSTT, were used to develop an algorithm and proposed clinical decision-making tool for transition from the Lokomat® to BWSTT in stroke, in line with three areas identified in previous literature: severity of impairment, assessment of assistance, and assessment of volitional control (Backus & Tefertiller, 2008; Behrman et al., 2005; Hornby et al., 2010; Hornby et al., 2005).

Of the 10 participants in the current study, four were clinically judged as ready for BWSTT therapy. The four participants that progressed on to BWSTT therapy had greater stroke acuity and concomitantly had completed less robotic sessions prior to inclusion into the study. Comparatively, participants judged as not-ready for BWSTT at the time of review, who were more days post-stroke and who had completed more Lokomat® sessions prior to study entry, never progressed on to BWSTT prior to discharge from their inpatient stay. This finding is consistent with another study reporting that an earlier post-stroke transition to BWSTT may be indicative of better and quicker recovery overall (Hornby et al., 2005). Furthermore, this variability in functional improvement highlights the ongoing unanswered questions of who does, and who does not, benefit from Lokomat® therapy, why is this the case, and the ongoing debate about when to stop use of the robotic if no further gains are being made. In review of the current study participants, those who were more days post-stroke, had more Lokomat® sessions, and did not progress onto BWSTT, included all of the haemorrhagic presentations as well as participants noted anecdotally to have aspects of cognitive deficit such as poorer insight or greater impulsiveness, greater sensory deficits including inattention or neglect, and increased tone. Despite these participants not making as many physical improvements, there is however, still benefit in use of the Lokomat® for CV exercise, as demonstrated in the first study.

At study entry, all participants had a FAC of 0 and had been completing Lokomat® therapy. This is consistent with the literature suggesting that robotics are more advantageous and should be used with mobility-dependent patients when the need for assistance is high and the FAC is below 4 (Backus & Tefertiller, 2008; Hornby et al., 2005; Mehrholz et al., 2017b). After the six CV exercise study sessions, when participants were reviewed regarding their ability to transition to BWSTT, the participants judged as not-ready for BWSTT were more likely to have an ongoing FAC of 0. That is, they still required the assistance from two therapists for mobility, were less likely to be able to

complete overground mobility, and most required the use of a rail. Comparatively, participants who were clinically judged as ready for BWSTT mostly had improved to a FAC of 1 and had generally started to complete some overground mobility with the help of only one person. The FAC score, as a measure of the degree of mobility impairment, aligns with severity, noted as the first broad concept in the literature regarding the ability to transition from the Lokomat® to BWSTT (Backus & Tefertiller, 2008; Behrman et al., 2005; Hornby et al., 2010; Hornby et al., 2005).

As such, severity forms the first section of the proposed algorithm and clinical decision-making tool, with study results included in the algorithm and tool suggesting continuation on the Lokomat® for those with a FAC of 0, and progression to the next step, assessment of assistance required, for those with a FAC of 1. The FAC of 1 to consider transition to BWSTT is lower than the previous recommendation of robotics for patients with a FAC of 3 or less (Mehrholz et al., 2013; Mehrholz et al., 2017b). However, a FAC of 1 does align with the fact that most contention of which modality to use, or when to transition from the Lokomat® to BWSTT, relates to patients who have some lower limb motor ability. To be consistent with the Cochrane reviews, the current algorithm and proposed clinical decision-making tool uses FAC as a concept of severity of mobility impairment, as compared to using a specific motor impairment scale, such as the ASIA scale for motor deficit in SCI used by Backus and Tefertiller (2008). The use of FAC is also similar to the use of FIM motor by Backus and Tefertiller (2008) and Hornby et al. (2005). A focus on overall level of mobility to determine ability to complete BWSTT was recommended by Hornby and colleagues (2005), who found retrospectively that no one individual outcome measure assessed on their three SCI patients, could clearly indicate when a patient was ready for BWSTT. Whilst Backus and Tefertiller (2008) and Hornby et al. (2005) both found that a FIM motor of 4 or above (patient providing 75% of assistance overground >50m and one person helping, or 17m independently) was related to an ability to complete BWSTT successfully, these studies were completed in SCI patients with bilateral deficits. Therefore, further work is required regarding the specific use of FAC versus FIM motor in stroke.

In the current study, while fitting the BWS harness, participants that were clinically judged as BWSTT ready completed the task of sit to stand with more independence, had better balance, and more even weight-bearing, as compared to those participants that were clinically judged as not-ready for BWSTT. Similarly, as compared to the not-ready for BWSTT participants, the participants that were BWSTT ready were noted to have more challenging Lokomat® settings with a BWS less than 30%, GF less than 30-35%, and speed at or above 2.0kph. Following on from the initial assessment of severity noted above, the next broad concept regarding modality choice and transition from the Lokomat® to BWSTT in the literature for patients with some lower limb motor

ability is how much assistance is required (Backus & Tefertiller, 2008; Hornby et al., 2005). As such, the second concept of the proposed algorithm and clinical decision-making tool is assessment of assistance required using a) clinical observation of the assistance required to complete the functional task of sit to stand and balance while weight bearing evenly for fitting the BWSTT harness, and b) the assistance required and provided through the Lokomat® settings. Essentially, the results included in the proposed algorithm and clinical decision tool suggest that patients noted to need supervision only, or no assistance with the functional tasks of sit to stand and standing, who balance with equal weight-bearing and require less assistance from the Lokomat® device (BWS<30%, GF<30-35%, speed >/=2.0kph), should progress onto assessment of volitional control. Conversely, the indication included in the tool is that patients needing assistance from at least one therapist for both sit to stand and standing, with uneven weight-bearing and more supportive Lokomat® settings, continue with the Lokomat®.

Previous work on transition from the Lokomat® to BWSTT in SCI has included clinical observations of the assistance required to support an upright trunk posture, as well as the leg in stance and swing, recommending continuation on the Lokomat® if assistance is required by more than one person, or multiple points of assistance are required (Backus & Tefertiller, 2008; Behrman et al., 2005; Hornby et al., 2005). This led to the inclusion of trunk posture and knee control in the current proposed decision-making tool as well as inclusion of assessment of sit to stand, standing balance and weight-bearing in the outcome measures. Similarly, while no specific details were given, the Lokomat® BWS and speed are noted by Hornby et al. (2005) as factors influencing ability to complete BWSTT. Interestingly, GF, which assists a patient's limb swing, was not mentioned. BWS while on the robotic particularly relates to maintaining adequate knee extension in stance, so is noted as one of the key concepts of the physiological gait pattern to be monitored and progressed during Lokomat® therapy as a patients' knee control improves (Hornby et al., 2005). Ada et al. (2010a) also note the speed with which a patient with stroke can swing their affected leg forward across the relative backward moving treadmill mat as influencing the success of completing BWSTT. The presented study results confirm this as an important consideration, with participants with faster limb movement, as well as faster BWSTT speeds (>1.0kph), being those judged as ready for BWSTT.

Participants considered capable of doing so were asked to complete a repeated lifting action of their affected leg (repeated maximal hip and knee flexion, described as the SALL test in Chapter 3) while standing in the BWS harness. Of the six participants that were physically able to attempt this action, the four that were clinically judged as BWSTT ready had more than 45 degrees of flexion at both the hip and knee joint, while the participants clinically judged as not-ready for BWSTT had

less than 45 degrees flexion at both joints. The ankle dorsiflexion range seemed less relevant with inconsistency between those that could progress to BWSTT and those that could not. Furthermore, an ankle-foot orthosis or electrical stimulation device could be used to accommodate a lack of dorsiflexion. One participant, who was clinically judged not-ready for BWSTT, was found in the BWSTT trial to have a BWS greater than the recommended 50% (Hesse, 2008) with ongoing knee flexion in stance averaging 30 degrees, pelvic drift for a third of steps, toe catch on more than 50% of steps taken, decreased symmetry of steps (>7cm), no heel strike, and a slower speed of limb movement and BWSTT speed. Compared to participants in the BWSTT ready group, these issues could not be assisted by verbal cueing or physical facilitation of one person, which is a consideration also included in the work by Behrman et al. (2005). The assessment of volitional control is the third of the three broad concepts in the literature, so was added as the third section of the proposed algorithm and clinical decision-making tool, including firstly the stationary SALL test, and secondly the dynamic BWSTT trial. The assessment of volitional control in a both static and dynamic situation is consistent with the work of Behrman et al. (2005), who reviewed stepping ability from a static and dynamic viewpoint to form their decision-making algorithm in SCI. As knee control in stance and toe clearance have been found to be important in physiological gait in robotic therapy (Hornby et al., 2005), these are two key factors to be taken into account when assessing readiness for BWSTT.

The stages of the proposed algorithm and clinical decision-making tool have been presented in the suggested order of review, however the components are not mutually exclusive, a concept supported by others (Backus & Tefertiller, 2008; Hornby et al., 2005). Furthermore, a patient can be progressed through as many stages of the algorithm and clinical decision-making tool as required until a clear decision is made, but with the likely outcomes represented at each section with regard to BWSTT readiness. For example, any patient with some volitional limb control could safely proceed to complete a trial of BWSTT, although this is likely to be unsuccessful if they are noted initially in the SALL test to have hip flexion and knee flexion less than 45 degrees, or had not previously progressed to a FAC of 1, improved functional independence, or low enough Lokomat® settings. Once a patient has attained a FAC of 1 the suggestion is to review the steps of the proposed clinical decision-making tool at each Lokomat® therapy session with similar recommendations for regular review made by others (Backus & Tefertiller, 2008; Behrman et al., 2005).

4.6 Discussion Summary

In summary, in adult patients with subacute stroke, sustained moderate intensity CV exercise, in line with recommended guidelines, can be achieved using the APF activities of the Lokomat®,

where optimal device settings are used and progressed as patients improve. The moderate intensity achieved was irrespective of the APF activity completed, such that therapist or participant choice of activity can be considered between the included APF activities. The BORG scale, whilst perhaps needing further investigation, was able to demonstrate clinical accuracy to represent CV workload at moderate intensities, however optimal device settings and use of the APF activities may be enough to drive CV workload. BWSTT, which also provides a CV training benefit, with potentially less risk of passive over-assistance and increased step variability, is recommended by the proposed algorithm and clinical decision-making tool to be reviewed for readiness at a FAC of 1. Conversely, patients with a FAC of 0 are recommended to continue with the Lokomat®, as are patients guided at various stages by the clinical decision-making tool relating to less observed functional independence during device set-up, less challenging Lokomat® settings, smaller ranges of active hip and knee flexion in standing, and increased need for assistance to achieve a physiological gait pattern in BWSTT. These patients recommended to continue on the Lokomat® will still benefit from CV exercise provided by completing the APF activities of the Lokomat® at optimal device settings, regardless of whether physical improvements are further gained.

4.7 Conclusions

Between the two studies the research completed had the following aims:

1. To determine: Can the Lokomat®, with use of the APF activities, be used to complete sustained moderate intensity CV exercise in patients with subacute stroke?
    a. Can a moderate intensity level of CV exercise be achieved using the APF activities?
    b. Is there a difference in the intensity achieved between different APF activities used?
    c. Can moderate intensity CV exercise be sustained for a minimum 10-minute duration?
    d. Do clinical changes in Lokomat® device settings influence the CV workload achieved?
    e. Does participant motivation and enjoyment influence CV workload outcomes?
    f. Can the CR-10 BORG scale be used clinically to ascertain intensity levels while completing APF activities on the Lokomat®?
2. To develop an algorithm and propose a clinical decision-making tool guiding progression from the Lokomat® to BWSTT in subacute stroke, based on criteria supporting the concepts of patient severity, amount of assistance required, and degree of volitional control.

From the results gained it may be concluded that, in mobility-dependent adults with subacute stroke:

- A moderate intensity of CV exercise can be achieved on the Lokomat® when using the Faster, Graph, and Gabarello 2 APF activities with optimal device settings, as applied in the current study.
- There is no difference in the CV intensity achieved between the three APF activities of Faster, Graph, and Gabarello 2, as used in the current study.
- A moderate intensity of CV exercise can be sustained for a minimum of 10 minutes, when completing locomotor therapy on the Lokomat®, using the included APF activities and optimal device settings, as applied in the current study.
- Lokomat® device settings of BWS and GF, when appropriately clinically progressed over two weeks, as applied in the current study, do not influence the CV workload achieved. Appropriate progression may still be required to maintain CV workload, and maximise challenge and mobility outcomes.
- Motivation toward the APF activity completed has an unknown influence on CV workload, as motivation scores were consistent across results and therefore an impact on CV workload could not be determined.
- Enjoyment is greatest for the Graph APF activity, as compared to the Faster or Gabarello 2 APF activities, however this difference in enjoyment does not influence CV workload outcomes.
- The BORG CR-10 scale can likely be used clinically to represent moderate intensity CV exercise, using either dyspnoea or affected-leg perceived effort, when completing the APF activities on the Lokomat® with optimal device settings, as applied in the current study.
- An algorithm and clinical decision tool can guide choice of locomotor therapy modality, and transition between the Lokomat® and BWSTT, based on decisions relating to severity of impairment, assessments of assistance required, and assessments of volitional control.
- Differences exist between patients ready versus not-ready for BWSTT, with BWSTT-ready patients having: a FAC of 1; independence with sit to stand and standing balance with even weight-bearing; Lokomat® BWS<30%, GF<30-35%, and speed >/=2.0kph; >45 degrees of active hip and knee flexion in standing with less than 50% BWS; no physiological gait issues during BWSTT that cannot otherwise be managed by assistance from only one therapist.
- Where the algorithm and clinical decision tool indicate ongoing use of the Lokomat®, CV exercise can still be achieved in line with recommended guidelines, indicating a benefit to ongoing Lokomat® use.

While a moderate intensity of CV exercise was equally achieved using the Faster, Graph, and Gabarello 2 APF activities, Hocoma have a number of other APF activities which are changed and updated on a regular basis. As such, current conclusions should not be interpreted to infer that all

other APF activities available on the Lokomat®, but not included in the current research, would equally lead to the same moderate intensity of CV exercise. The conclusion from the current research is that the three tested APF activities can equally lead to moderate intensity CV exercise in mobility-dependent patients with subacute stroke, and that future software development could aim to include assurance of this capability. Moreover, enjoyment may be greater for other APF activities not included within the current research, with the achievement of CV exercise, or an alternate therapy goal needing consideration regarding APF activity choice.

Similarly, while the current study concludes a sustained moderate intensity can be achieved in mobility-dependent patients with subacute stroke, this does not imply this is achievable for all patients with stroke, for example in more mobile patients, with differing cognition levels, or those in a chronic phase. Use of the BORG CR-10 scale, demonstrated as able to represent moderate intensity exercise, would, however, assist in determining likely achievement of moderate intensity for other patient presentations, who are able to complete the scale. Given the intensity of CV exercise achieved was moderate for all three included APF activities completed at optimal device settings, use of the BORG scale may also not be required if the greatest possible level of challenge, via device settings and use of the APF activities, is provided to the patient. Optimal device settings in the current study were used, and progressed, under the guidance of an experienced advanced Lokomat® practitioner, such that results should also not be considered replicable by less experienced users of the Lokomat®.

Furthermore, while the clinical progression of Lokomat® device settings did not influence CV workload in the current study, this does not imply that reducing BWS and GF, and increasing speed, does not influence CV workload. Rather, that the amount of change in device settings made within the current study did not achieve this. The goal, as previously stated, of Lokomat® CV training is to increase the CV fitness capacity of patients with stroke, which may have occurred in the current study further limiting the ability to assess the impact of the change of device settings. Investigation overtime of the impact on CV workload from a variance in Lokomat® settings with concurrent use of the device is therefore less valid, as compared to an individual assessment time, or multiple assessments spaced without concurrent training. Both are difficult to achieve in a clinical setting, as are reviewing multiple device settings in a mobility-dependent population such as stroke, where particular device settings are required for a physiological gait to be maintained.

The presented algorithm and clinical decision tool were developed with reference to participants progressing from an initial FAC of 0 to a FAC of 1. That is, the current study participants were the most mobility-dependent patients who were also in the subacute phase post-stroke. Furthermore, all participants had a level of cognition to be able to follow instructions and feedback well. As such, the proposed algorithm and clinical decision tool may not apply to more mobile patients, or those with cognitive challenges, or patients within the chronic phase post-stroke.

4.8 Strengths and Limitations

Whilst only having a total of 10 participants, the CV exercise component of the study used a repeated measures design, with each participant completing six study sessions, and within each session three APF activities were completed. In total therefore, each APF activity was completed six times per participant for a total of 18 APF sessions per participant. Randomisation of the order of the APF activities across the six study sessions accounted for all possible permutations negating any order or combination effects. As such, 10 participants were planned to complete 180 data points for comparison of CV workload on the APF activities, whereby 56 of 60 planned study sessions and 168 of the 180 planned APF activity sessions were completed. With no prior comparative research a power calculation was not completed, however the planned 180 data points, 60 for each APF activity, were considered adequate. Furthermore, the metabolic data was taken as a mean over the full fourth minute, and therefore was an average of six COSMED® VO_2 readings. In comparison, the inclusion of only 10 participants for the transition from the Lokomat® to BWSTT was a limitation for this preliminary research. More participants would have possibly created greater evidence for delineation of decision points that could have perhaps also been tested statistically. Data collected using the P&O software did however, include repeated measures with an average of five lifts in the SALL test and nine gait cycles in the BWSTT trial.

The majority of participants were male (8:2) with a good level of cognition required to complete consent processes. This raises the question of how applicable results may be to female patients as well as to a less cognitively competent patient cohort. Cognition is a factor mentioned by Koenig et al. (2011) that may influence outcomes regarding CV workload on the Lokomat®. The current cohort could consciously participate as actively as possible during testing of the CV workload, and could follow instructions well for the assessments associated with the transition to BWSTT. Hence, the effectiveness of robotics to achieve sustained moderate intensity CV exercise, as well as validity of the decisions in the algorithm and clinical tool would need further investigation in less cognitively competent patients.

Participants in the current study were also selected on a basis of convenience whereby all eligible patients attending the Lokomat® robotic for therapy at the study facility were considered, with those volunteering to participate therefore potentially being motivated and interested to do so. Participants therefore also knew the Principle Investigator of the current study, who was the study facility's lead Lokomat® clinician. This adds a potential for bias, particularly with regard to the subjective outcomes such as BORG, motivation and enjoyment, but also as to how much active effort participants may have put into their Lokomat® CV exercise study sessions. Participants may have also felt a need to engage more so than otherwise in the process for transition to BWSTT. The experience of the Principle Investigator in using the Lokomat® was, however, considered to outweigh this with regard to being able to set the most challenging (optimal) device settings, as well as make a sound clinical judgement regarding readiness for BWSTT based on years of experience.

Participants were not blinded as it was impossible to do so, and all measures were intended to be collected within a clinical therapy session by the Principle Investigator. In this context, it was believed that the primary outcome measure for the CV exercise being objective and measured by the COSMED® device outweighed this potential limitation. The research also purposely intended to be an analysis of workload achieved in a typical clinical therapy session, without variance to usual clinical procedure. Standardised clinical protocols were used and participants were not informed of prior achieved session workloads, or the clinical judgement made regarding the SALL test or BWSTT trial. Given the goal of not interrupting clinical therapy and the unavailability of additional resource for safety, a CPET could not be feasibly completed on the current participants. Completion of a CPET would have strengthened results, rather than comparison to participants from another study, however as discussed maximal oxygen consumption results across previous studies in stroke are relatively similar and still indicate a moderate intensity of CV exercise. Compared to the data collected for CV exercise, data for the transition to BWSTT was much more subjective, gathered through clinical observation and analysis was completed by observational comparison without statistical analysis. The use of FAC, Lokomat® settings, and video analysis for gait biomechanics possibly strengthen results.

The BORG CR-10 scale, while recommended in previous literature, and perhaps easier to understand regarding the spread of data points, did not allow for worthwhile correlation with VO_2. While clinically BORG results demonstrated moderate intensity, correlation completed was weak, although this was potentially expected given the scale of the BORG RPE CR-10. The motivation and enjoyment scores also had a small scale, using a self-designed Likert scale from 1 to 5. Investigation into alternative options, such as the centiMax BORG, or reliable and validated tools

for motivation and enjoyment, may have been beneficial. Standardised questions for the BORG, motivation, and enjoyment scores, were used, however motivation scores had no variance in results such that the impact of motivation on CV workload cannot be assessed. Similarly and previously mentioned, Lokomat® settings were progressed as per usual clinical practice, within a short time frame, and over time. As such, the impact of changing the Lokomat® settings on CV workload was possibly also not able to be well assessed. Furthermore, only three of the available APF activities were reviewed, meaning results cannot be extrapolated to other APF activities or outside of mobility-dependent subacute stroke patients.

4.9 Future Research

A range of future research options include:

- Assessment of participants' lower limb strength for exploration of relationships to both CV workload and transition to BWSTT. Despite all participants having the same FAC on study inclusion, there was variability amongst participants with regard to the amount of affected-leg muscle recruitment, noted through observation of the assistance required by the participant during preparation for their Lokomat® session. This was not objectively measured in either component of the current study, but has implications for VO_2 outcomes and transition to BWSTT, and as such, warrants further investigation.
- CV workload achieved with the use of the APF activities with more experienced, versus less experienced Lokomat® therapists. The device is complex, and confidence to set optimal device settings to maximise CV workload comes with practice and repeated use of the device with a range of patients. CV workload, clinical gait outcomes, patient comfort and satisfaction could all be areas for further investigation stratified by time of Lokomat® use of the practitioner.
- Randomised controlled trials comparing Lokomat® and early transition to BWSTT therapy for CV workload and clinical gait outcomes. Speed may need to be decreased, and BWS increased, for a successful transition to BWSTT to occur. This may have a negative impact on CV workload and potentially impact modality choice, therefore warranting investigation. Ongoing research into clinical gait outcomes for therapy efficacy between the two modalities is also required. This would preferably be completed in a randomised way, using a tool such as the proposed decision-making tool to guide readiness for BWSTT, at which point randomisation to ongoing Lokomat® versus BWSTT could occur. Split sessions of Lokomat® and BWSTT therapy could also provide an ethical option whereby current research remains uncertain regarding the best treatment option.
- Options to increase CV intensity. Current study CV intensity results were presented as a mean, with a previous study indicating 40% of stroke participants on the Lokomat® reached

a moderate intensity using mechanical torque feedback similar to the Graph APF's. Currently there is no certainty as to what drives the level of CV workload on the Lokomat® although BWS, GF, and speed are potential options needing further investigation. Options such as the use of path control, removal of hands from the rails of the device, or lessened trunk support may also warrant investigation as potential options for increasing CV workload. GF settings in the current study were maintained on a bilateral setting whereby review of the impact of split limb GF settings and CV workload would also be of interest.

- The centiMax BORG scale, which has 100 points, could be investigated for increased correlation to VO_2, as well as feasibility of use on the Lokomat® in the stroke population, and any benefit over the CR-10 BORG scale used in the current study.
- Assessment of other APF activities of the Lokomat®. As mentioned, the Lokomat® comes with a range of other APF activities that are also continuously changed and updated. Assessment of the CV workload, as well as motivation and enjoyment of these other APF activities is warranted. Use of validated motivation and enjoyment scores could also be considered.
- Assessment of a range of patient presentations including more females, patients with a range of cognitive and mobility levels, and patients in the chronic phase of stroke. Current results are only applicable to mobility-dependent patients in the subacute phase post-stroke who have a good level of cognition. Participants of the current study were also mostly male.
- Use of Electromyography (EMG) to monitor activity of the affected side for sustained use, as well as the combined benefits of Functional Electrical Stimulation (FES) with either Lokomat® or BWSTT use. Whilst current study participants rated their perceived affected-leg use, monitoring with EMG would provide additional benefit, as well as interest regarding comparison to use of the BORG scale for perceived leg effort. The addition of FES would be of interest in decreasing Lokomat® settings to increase CV workload, or additionally to review the impact regarding early transition to successful BWSTT.
- The repeatability, reliability and validity of the proposed clinical decision tool. The proposed tool has not been tested across a larger number of patients, or with a range of different therapists. A repeated inter-therapist process using the algorithm or clinical decision tool in patients with stroke would further validate or refine sections. Review regarding the addition within assessment of assistance required for knee control in stance, potentially by using a bilateral marching action in the SALL test, would be of particular interest, as would further exploration of toe-off and toe catching. Review of general mobility assessments such as the FIM motor versus FAC or other such options could also be warranted.

APPENDICES

APPENDIX 1:
ETHICS, PARTICIPANT INFORMATION SHEET AND CONSENT

A1.1 Ethics Approval Letter

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Government of South Australia
SA Health
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Final Approval for Ethics Application

2 August 2017

Dr Christopher Barr
Senior Lecture
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Dear Dr Christopher Barr

OFR Number:	115.17
HREC reference number:	HREC/17/SAC/198
Project title:	Does clinical use of the Augmented Performance Feedback options of the Lokomat® enable cardiovascular exercise in the subacute adult stroke population attending rehabilitation?
Chief Investigator:	Dr Christopher Barr

Ethics Approval Period: 26 July 2017 to 26 July 2020

The Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188) have reviewed and provided approval for this application which appears to meet the requirements of the *National Statement on Ethical Conduct in Human Research (2007).*

You are reminded that this letter constitutes **Ethics** approval only. **Ethics approval is one aspect of the research governance process.**

You must not commence this research project at any SA Health sites listed in the application until a Site Specific Assessment (SSA), or Access Request for data or tissue form, has been approved by the Chief Executive or delegate of each site.

Public health sites approved under this application:

- Repatriation General Hospital
- Flinders Medical Centre

The below documents have been reviewed and approved:

- Low and Negligible Risk (LNR) Research form dated 29 May 2017
- Participant Information Sheet/Consent Form v1 dated 27 March 2017
- Data collection record v1 dated 16 May 2017
- Questionnaire v1 dated 16 May 2017

Terms And Conditions Of Ethics Approval:

As part of the Institution's responsibilities in monitoring research and complying with audit requirements, it is essential that researchers adhere to the conditions below and with the *National Statement chapter 5.5.*

Final ethics approval is granted subject to the researcher agreeing to meet the following terms and conditions:

1. The approval only covers the science and ethics component of the application. A SSA will need to be submitted and authorised before this research project can commence at any of the approved sites identified in the application.
2. If University personnel are involved in this project, the Principal Investigator should notify the University before commencing their research to ensure compliance with University requirements including any insurance and indemnification requirements.
3. Compliance with the *National Statement on Ethical Conduct in Human Research* (2007) & the *Australian Code for the Responsible Conduct of Research* (2007).
4. To immediately report to SAC HREC anything that may change the ethics or scientific integrity of the project.
5. Report Significant Adverse events (SAE's) as per SAE requirements available at our website.
6. Submit an annual report on each anniversary of the date of final approval and in the correct template from the SAC HREC website.
7. Confidentiality of research participants MUST be maintained at all times.
8. A copy of the signed consent form must be given to the participant unless the project is an audit.
9. Any reports or publications derived from the research should be submitted to the Committee at the completion of the project.
10. All requests for access to medical records at any SALHN site must be accompanied by this approval email.
11. To regularly review the SAC HREC website and comply with all submission requirements, as they change from time to time.
12. Once your research project has concluded, any new product/procedure/intervention cannot be conducted in the SALHN as standard practice without the approval of the SALHN New Medical Products and Standardisation Committee or the SALHN New Health Technology and Clinical Practice Innovation Committee (as applicable). Please refer to the relevant committee link on the SALHN intranet for further information.

For any queries about this matter, please contact Petrina Kasperski on (08) 8204 7433 or via email to Health.SALHNOfficeforResearch@sa.gov.au.

Yours sincerely

A/Professor Bernadette Richards
Chair, SAC HREC

A1.2 Ethics Approval Letter – Site Specific Approval

Final Approval for Governance SSA Application

Ms Nicole Prideaux,

Physiotherapist, RGH

Dear Ms Nicole Prideaux

OFR Number:	115.17
HREC reference number:	HREC/17/SAC/198
SSA reference number:	SSA/17/SAC/301
Project title:	Does clinical use of the Augmented Performance Feedback options of the Lokomat® enable cardiovascular exercise in the subacute adult stroke population attending rehabilitation?
Chief Investigator:	Ms Nicole Prideaux
Site(s):	RGH & FMC
Ethics Approval Period:	26 July 2017 to 26 July 2020

On the basis of the information provided in your Site Specific Assessment submission, I am pleased to inform you the SALHN Chief Executive Officer has granted approval for this study to commence at the above nominated site(s).

You are reminded that this letter constitutes **Governance** approval only. **Governance approval is one aspect of the research governance process**.

You must not undertake the research project at any SA Health sites listed in the application without a valid Ethics Approval, or an Access Request for data or tissue form has been approved, by an appropriately registered and certified Human Research Ethics Committee (HREC).

The below documents have been reviewed and approved:

- Low and Negligible Risk (LNR) Research form dated 29 May 2017
- Participant Information Sheet/Consent Form v1 dated 27 March 2017
- Data collection record v1 dated 16 May 2017
- Questionnaire v1 dated 16 May 2017
- confidentiality_agreement_C_Barr
- Confidentiality_agreement_C_Drummond
- ConfidentialityAgreement_SAHLN_MB
- Co-Principal Investigator Agreement 3May2017
- 115.17 SAC HREC Approval letter 2Aug2017

HREC reviewed documents listed on the approval letter are accepted as part of the site authorisation.

The SSA reference number should be quoted in any correspondence about this matter.

If University personnel are involved in this project, the Principal Investigator should notify the University before commencing their research to ensure compliance with University requirements including any insurance and indemnification requirements.

TERMS AND CONDITIONS OF ETHICS AND GOVERNANCE APPROVAL

As part of the Institution's responsibilities in monitoring research and complying with audit requirements, it is essential that researchers adhere to the conditions below and with the *National Statement chapter 5.5.*

- If University personnel are involved in this project, the Principal Investigator should notify the University before commencing their research to ensure compliance with University requirements including any insurance and indemnification requirements.
- Compliance with the National Statement on Ethical Conduct in Human Research (2007) & the Australian Code for the Responsible Conduct of Research (2007).
- To immediately report to the Office for Research anything that may change the ethics or scientific integrity of the project.
- Report Significant Adverse events (SAEs) as per SAE requirements available on the Office for Research website.
- Submit an annual report on each anniversary of the date of final approval and in the correct template from the Office for Research website.
- Confidentiality of research participants MUST be maintained at all times.
- A copy of the signed consent form must be given to the participant.
- Any reports or publications derived from the research should be submitted to the Committee at the completion of the project.
- All requests for access to medical records at any SALHN site must be accompanied by this approval letter.
- Once your research project has concluded, any new product/procedure/intervention cannot be conducted in the SALHN as standard practice without the approval of the SALHN New Medical Products and Standardisation Committee or the SALHN New Health Technology and Clinical Practice Innovation Committee (as applicable). Please refer to the relevant committee link on the SALHN intranet for further information.
- Researchers are reminded that all advertisements/flyers need to be approved by the committee, and that no promotion of a study can commence until final ethics and executive approval has been obtained. In addition, all media contact should be coordinated through the FMC media unit.

Should you have any queries about the consideration of your Site Specific Assessment form, please contact the Office for Research on 8204 6453 via email: Health.SALHNOfficeforResearch@sa.gov.au.

Yours sincerely

Simon Windsor

Research Governance Officer, Office for Research

A1.3 Participant Information Sheet and Consent Form

Government of South Australia
SA Health

Participant Information Sheet/Consent Form

Non-Interventional Study - *Adult providing own consent*

Repatriation General Hospital (and future FMC rehabilitation campus)

Title	Does clinical use of the Augmented Performance Feedback activities of the Lokomat® enable cardiovascular exercise in the subacute adult stroke population attending rehabilitation.
Short Title	Does use of the interactive activities of the Lokomat® cause aerobic exercise in adults following stroke.
Coordinating Principal Investigator/ Principal Investigator	Christopher Barr
Associate Investigator(s)	Maayken van den Berg, Claire Drummond, Nicole Prideaux
Location	Repatriation General Hospital

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project, Does use of the interactive activities of the Lokomat® cause aerobic exercise in adults following stroke. This is because you have had a stroke and are using the Lokomat® robotic device at the Repatriation General Hospital. The research project is aiming to understand if cardiovascular exercise can be achieved using the activities available on the Lokomat®, and if so, which of the available activities is best. We also wish to measure the quality of your walking when you stop using the Lokomat®.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and research involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read

• Consent to take part in the research project

• Consent to the tests and research that are described

• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The aim of this research project is to determine if cardiovascular exercise can be achieved using the activity options of the Lokomat® and whether there is a difference between the activity options available. We will also aim to review how to best measure an effective level of exercise, your perspectives on the training and parameters that may help us determine when you are ready to progress to therapy without the robotic assistance. This project applies to adults shortly after their stroke who are attending rehabilitation at the Repatriation General Hospital (to be re-located to FMC rehabilitation campus).

Currently we know cardiovascular exercise is a very important component of rehabilitation following a stroke but we have limited ways to achieve it. The Lokomat® is a robotic walking device that will assist you to walk on a treadmill following your stroke. It is used as part of the rehabilitation program for people following a stroke at the Repatriation General Hospital. The Lokomat® provides a potential option for cardiovascular exercise however currently we do not know if we are achieving cardiovascular exercise while completing the activities available on the Lokomat®.

This study will help to determine if we are meeting the need of providing cardiovascular exercise to people who have had a stroke and are using the Lokomat® as part of their rehabilitation. Further it will help determine if particular activities available on the Lokomat® are best for achieving cardiovascular exercise, how best to measure this, what participants preferences are and when someone may be ready to progress to not using the robotic.

The results of this research will be used by the study investigator, Nicole Prideaux, to obtain a Masters of Clinical Rehabilitation degree.

This research has been initiated by the study investigator, Nicole Prideaux – Physiotherapist Repatriation General Hospital.

This research is being conducted by SA Health in collaboration with the Flinders University of South Australia.

3 What does participation in this research involve?

At the Repatriation General Hospital all people admitted with a stroke are currently considered by their usual ward physiotherapist for treatment with the Lokomat® robotic therapy device. If your ward physiotherapist decides with you that using the Lokomat® robotic device would be in your best interests as part of your rehabilitation program you will be referred onto this service as part of standard care at RGH.

If you meet the eligibility criteria for the research you will be asked by your ward physiotherapist (or another staff member not involved with the research project) if you would like to discuss the project with the study investigator, Nicole Prideaux. If you agree, Nicole will come to discuss the research project with you. The consent form will be explained, signed and a copy given to you prior to any study assessments being performed.

When accessing Lokomat® therapy all patients currently complete activities that are included as part of the Lokomat® device. As part of the study we would like to measure how hard you are working – your cardiovascular exercise level – while completing these different activities on the Lokomat®. We have chosen 3 activities of the Lokomat® to test. The treatment you will receive as part of the study is no different to the treatment you would receive if you are not in the study, the only difference is that we are measuring how hard you are working.

To measure how hard you are working while on the Lokomat® and completing the 3 different activities you will be fitted with a face mask that does not alter your breathing in anyway but does analyse your breathing for us. You will also be asked to rate the level of how hard you feel you are working. Finally you will be asked to rate the different activities completed to get your perspectives

on the training. This will happen over 6 of your Lokomat® treatment sessions after which you can continue with your Lokomat® treatment without any further such measures being taken. No extra time is required, all measures are completed within your normal treatment sessions using the Lokomat®. Each session the order of the activities you will complete will vary to account for fatigue and training parameters set on the Lokomat® will be recorded.

The Lokomat® gives you the opportunity to practice walking with harness support, and in addition the robotic gait orthosis provides assistance to gait movements. With independent walking as primary goal of Lokomat therapy, a logical progression of Lokomat training is bodyweight supported treadmill training. This means walking on the treadmill with a harness to support your body weight, but without receiving robotic assistance to support your leg movement. When the treating clinician thinks you are ready for this, you will be given the opportunity to practice walking by bodyweight supported treadmill training (by removing the gait orthosis from the Lokomat). The data we get from this will help to provide therapists with clinical guidance on when patients are ready to progress from the Lokomat to bodyweight supported treadmill training.

When your treating therapist thinks you are ready to transition to body weight supported treadmill training (walking with the support of a harness but without the robotic assistance) we will measure the quality of your leg movements by either a video recording of your legs, or by putting small sensors on your legs that detect the movement of your lower limbs.

Data collection will continue for 5 months at the Repatriation General Hospital however you will only need to participate for the duration of 6 sessions during your therapy, and one recording session at the end of your use of the Lokomat. Information will be stored on the secure SA Health internal hard-drives which require a specific log on by the Principle Investigator.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

There are no costs associated with participating in this research project, nor will you be paid or reimbursed.

4 What do I have to do?

There are no changes to your usual care provided as part of your rehabilitation program at the Repatriation General Hospital by participating in this study. You can participate in all your scheduled other therapy and continue to take all prescribed medications as per your treating team.

If you agree to participate in the study you are not required to do anything extra to your usual therapy. The only addition is wearing the facemask, answering questions relating to how hard you

are working and if the treating therapist thinks you are ready for it we will record your movements whilst walking on the treadmill while being body-weight supported, but without being robotic-assisted.

5 Other relevant information about the research project

There will be ten participants in total in the study, all completing the six measured sessions on the Lokomat® as part of their usual rehabilitation care. All participants will be treated equally. The study is being completed at the Repatriation General Hospital in collaboration with the Flinders University.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Repatriation General Hospital.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital either with or without the Lokomat® robotic device.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research, however possible benefits may include direction on how to best achieve cardiovascular exercise for yourself and future stroke patients using the Lokomat® as well as determining guidelines for readiness to progress therapy to non-robotic supported treadmill walking.

9 What are the possible risks and disadvantages of taking part?

This research project does not introduce any additional risks to your usual care. You may feel a slight discomfort when wearing the mask during the exercises. You are free to stop using the mask and withdraw your participation at any time.

10 Can I have other treatments during this research project?

Whilst you are participating in this research project, you can continual all usual treatments as part of your ongoing rehabilitation plan.

11 What if I withdraw from this research project?

If you decide to withdraw from this research project, please notify a member of the research team before you withdraw. A member of the research team will inform you if there are any special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the principle investigator and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the principle investigator up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

12 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include an issue with the Lokomat® and/or unavailability of the principle investigator.

13 What happens when the research project ends?

Once you have completed your six sessions where measures are taken while completing the Lokomat® activities you will be able to continue to use the Lokomat® and receive all usual care as per your rehabilitation goals and plan.

Part 2 How is the research project being conducted?

14 What will happen to information about me?

By signing the consent form you consent to the principle investigator and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. The data will be re-identifiable (you will be allocated a participant number) with a list of personal details connected to the participant number stored separately that only the study investigator, Nicole Prideaux, will have access to. Only the investigation team whose details are included below will have access to the data. The data will be stored in the secure SA Health hard-drive system of the study investigator necessitating a personalised log on to access it. The data will be stored for 1 year after which it will be deleted. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the research team accessing health records if they are relevant to your participation in this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Confidentiality will be maintained through use of the participant number only in this situation.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and/or South Australian privacy and other relevant laws, you have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project and for potential future research described in Section 16 that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

15 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In the event of loss or injury, the parties involved in this research project have agreed to inform the treating team as part of your rehabilitation program at the Repatriation General Hospital.

16 Who is organising and funding the research?

This research project is being conducted by Nicole Prideaux – Physiotherapist at The Repatriation General Hospital in collaboration with Flinders University.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

17 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Southern Adelaide Local Health Network.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

18 Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the study investigator on 8275 1787 or any of the following people:

Clinical contact person

Name	Nicole Prideaux
Position	Principle Investigator – Physiotherapist, Repatriation General Hospital
Telephone	8275 1787
Email	nicole.prideaux@health.sa.gov.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	Villis Marshall
Position	Director, Office for Research
Telephone	8204 6453 / 0466 393 503
Email	Health.SALHNOfficeforResearch@sa.gov.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Southern Adelaide Clinical
Position	Executive Officer
Telephone	8204 6453
Email	Health.SALHNOfficeforResearch@sa.gov.au

Local HREC Office contact (Single Site -Research Governance Officer)

Name	Southern Adelaide Local Health Network
Position	Research Governance Officer
Telephone	8204 6453
Email	Health.SALHNOfficeforResearch@sa.gov.au

Consent Form - *Adult providing own consent*

Title	Does clinical use of the Augmented Performance Feedback activities of the Lokomat® enable cardiovascular exercise in the subacute adult stroke population attending rehabilitation.
Short Title	Does use of the interactive activities of the Lokomat® cause aerobic exercise in adults Accessing rehabilitation early on following stroke.
Coordinating Principal Investigator/ Principal Investigator	Christopher Barr
Associate Investigator(s)	Maayken van den Berg, Claire Drummond, Nicole Prideaux
Location	Repatriation General Hospital

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

I understand that, if I decide to discontinue the research project treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Principle Investigator/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature

APPENDIX 2:
EQUIPMENT

A2.1 The Lokomat® Robotic

Available since 2001, the Lokomat® robotic (Hocoma AG Switzerland, Lokomat® User Manual and Augmented Performance Feedback Supplement) is an exoskeleton robotic originally developed with regard to SCI patients and has been further developed to train gait ability in any patient with a gait deficit (Figure 4). The device includes a body weight supporting harness with an adjustable (via hardware and software) robotic orthosis positioned over a treadmill, allowing assisted, repetitive, task specific walking practice. Features that can be adjusted to target training to the individual include BWS, GF, and speed, as well as use of the biofeedback system and APF activities described below. The system available at the Repatriation General Hospital/Flinders Medical Centre Rehabilitation was the Lokomat® Pro version 6 (software 6.4.2.2).

Figure 4: The Lokomat® Robotic (Picture: Hocoma Switzerland)

Body-Weight Support: A dual system of static or dynamic BWS is available to off-load weight from the patient's legs allowing a supported physiological gait pattern to be maintained. By providing BWS the patient does not need to work as hard to hold themselves upright against gravity, assisting maintenance of an upright position for a longer duration and allowing participation in the walking action. The BWS is provided via the patient and orthotic ropes of the Lokomat® with the

goal of providing dynamic BWS, which allows for the natural vertical displacement of the gait cycle. The patient rope of the BWS system attaches to the patient harness and can also be used without the robotic orthosis in BWSTT. The least amount of BWS which still allows for a normal physiological gait pattern, with particular regard to knee extension in the stance phase of gait, should be provided clinically to maximise therapeutic benefits, and progress patients toward overground walking without BWS.

Guidance Force: GF relates to the amount the robotic orthosis assists or guides the patient's leg movements in the swing phase of gait. At a lower GF there are less forces from the orthosis acting upon the limb(s) of the patient such that the patient can alter the trajectory of the robotic orthosis, and must use more of their own effort/ability to maintain a physiological gait pattern. GF can be varied between zero and 100 percent of the device's capacity. At 100 percent a patient can be relatively passive and still achieve a physiological looking gait pattern. As such a lower (as low as possible) GF is best used clinically to challenge the participant, to ask them to work harder, and ensure more active participation.

Speed: The speed of the treadmill and robotic can be varied between 0.5 to 3.2 km/h to ensure a challenging session with higher speeds (whilst still maintaining a physiological gait pattern throughout the entire duration). If the orthotic is not in use, as in BWSTT, higher treadmill speeds can be used.

Biofeedback: The orthosis of the Lokomat® has sensors associated with the hip and knee joints. The sensors are able to monitor the forces the patient is applying, which are then represented as biofeedback units of real time patient activity. The biofeedback units are presented and tracked in a line graph for each of the right and left hip and knee joints, with separate line graphs for swing and stance phases of gait. The tracking of the biofeedback allows for monitoring of patient activity and has input towards outcomes within the APF activities as indicated below.

Augmented Performance Feedback: The Lokomat® software comes with a range of APF activities where the patient either controls an avatar on the patient screen through the activity of their legs, as monitored by the biofeedback system, or alternatively, a direct view the biofeedback graphs can be presented. This creates a virtual reality, game-based environment to measure and provide feedback to the patient regarding their limb use and performance. The APF activities are designed

for a specific purpose such as timing and symmetry, and are also intended to provide motivation, engagement, and possibly enhance enjoyment. Both the patient's use of their lower limbs to help move the orthosis, as well as the timing of their assistance within the gait pattern are important aspects used to alter outcomes within the APF activities. Three common APF activities used at the Repatriation General Hospital/Flinders Rehabilitation were chosen at a low to mid range level of cognitive complexity, with the greatest ability to have a varied GF according to Hocoma instructions. Namely these activities are:

- Graph APF: The patient's lower limb activity is represented in a line graph which can be shown to them on the patient screen (Figure 5). The graph responds in real time to the patients attempted leg movement with a bigger deviation in the line graph, and higher placement of the graph, providing feedback of more leg activity timed with the movement of the orthosis.

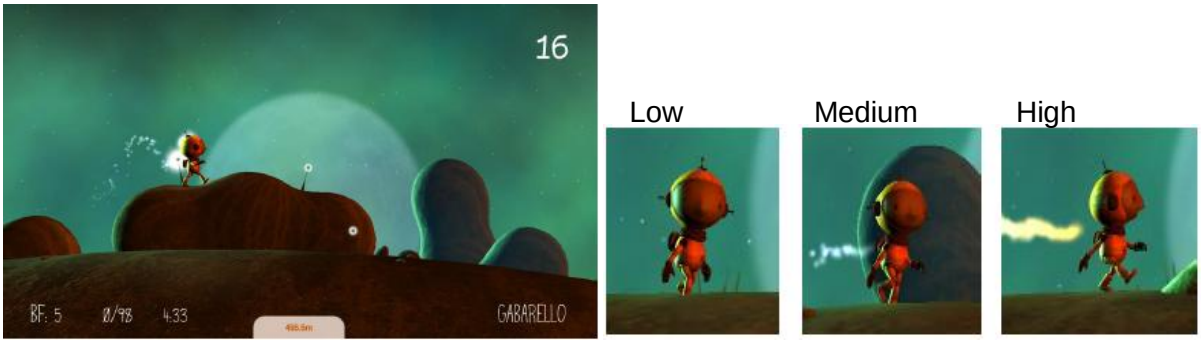
Figure 5: Graph Augmented Performance Feedback (Picture: Hocoma Switzerland)

- Faster APF: In the Faster APF activity the patient controls an avatar on the patient screen that is in a race against a series of consecutive computer controlled robots to collect the most coins (Figure 6). By utilising their lower limbs more actively the patient can beat the computer controlled robot to the coins and win the race.

Figure 6: Faster Augmented Performance Feedback (Picture: Hocoma Switzerland)

- Gabarello 2 APF: In the Gabarello 2 APF activity the patient attempts to help ‘Nicolo’, an alien avatar, collect flowers. In order to do this the patient has to use their legs actively to keep Nicolo’s jet pack ‘on high fire’ so he can race along as quickly as possible to collect flowers (Figure 7). Points are rewarded according to how many flowers are collected combined with the degree of activity of the lower limbs represented by keeping the jet pack on low, medium or high fire.

Figure 7: Gabarello 2 Augmented Performance Feedback (Picture: Hocoma Switzerland)



A2.2 The COSMED K5® system

The COSMED K5® system (COSMED K5, Italy, User Manual, V edition 05/2016) is a portable/wearable metabolic testing unit designed to measure cardio-respiratory and metabolic function during a range of activities. It can be used to analyse VO_2, carbon dioxide production, ventilation, HR, and energy expenditure. The device consists of a reusable silicone facemask connected via a flowmeter, external sensors, and tubing, to the portable base unit that completes analysis and records and stores data (Figure 8). The base unit can also wirelessly, or via USB cable, transfer the collected data to a computer with COSMED® software installed. Key components of the COSMED K5® system are described below.

Figure 8: The COSMED K5®

Reusable silicone face mask: The lightweight and flexible silicone face mask has inspiratory valves designed to minimise inspiratory resistance and a head cap to hold the face mask to the patients face.

Turbine flowmeter assembly: This assembly attaches to the facemask and consists of a bidirectional turbine, an optoelectronic reader (to measure infrared light interruptions caused by the spinning blade inside the turbine) and a wind cover (Figure 9). The sampling line is connected from the wind cover to the base unit and the turbine cable is connected from the optoelectronic reader to

the base unit. Daily calibration of the turbine is not necessary, but regular calibration is suggested to assure accurate measurements. For the purpose of the research calibration was completed daily in the room where testing was completed. Flowmeter specifications: Digital Turbine, 0.08-16 l/s Flow Range, +/-2% or 50ml/s Accuracy, <0.6cmH2O s/l @14 l/s Resistance.

Figure 9: Turbine Flowmeter Assembly (Picture: COSMED, Italy)

“removed as per copyright”

Base unit: The base unit contains the oxygen and carbon dioxide analysers, the sampling pump, transmitter, barometric sensors and electronics and is powered by a rechargeable removable enclosed battery. The unit allows for individualised participant data to be collected and stored against de-identified study participant details, gas and turbine calibration, test execution with internal data storage and data management along with transfer of data to a PC. The screen of the base unit includes a timer which records the duration of each test and data points are captured every 10 seconds.

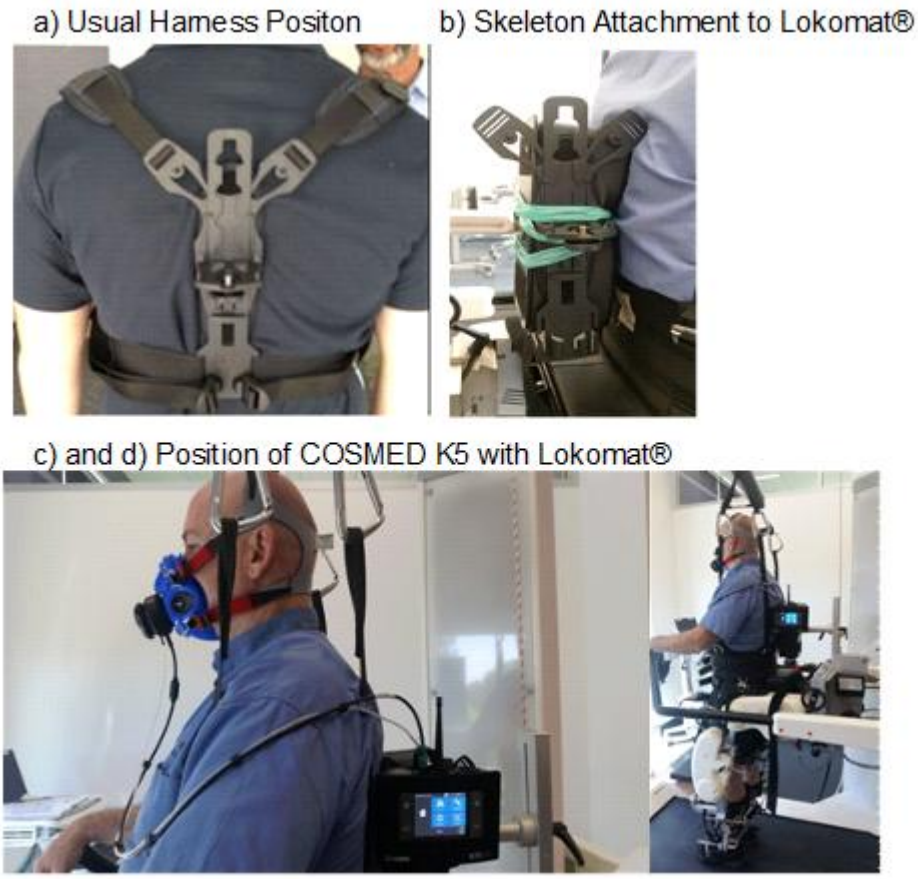
O2 Sensor: Housed within the base unit the O2 sensor measures the O2 concentration in the sample of gas provided to the device. Specifications: GFC 0-100% range, +/-0202 Accuracy, approx 120 ms response time.

CO2 sensor: Housed within the base unit to measure CO2 concentrations. Specifications: Digital NDIR, 0-10% range, +/-0.02% Accuracy, approx 100 ms response time.

Participant harness: A more rigid “skeleton” piece with an integrated screw in tripod mount for the base unit is combined with soft detachable straps ordinarily used to attach the base unit to the upper back of the participant (Figure 10). Overall the portable unit is light weight (900g battery

inserted) with the preferred position for testing being to use the harness to secure the base unit to the upper back of the participant. Due to participants in the current research being within the Lokomat®, the skeleton of the COSMED K5® harness was secured just behind the participant via removable straps to the Lokomat® frame (Figure 10). As such the participant was not carrying the weight of the base unit whilst still closely maintaining set-up to the usual and preferred position recommended by the manufacturer.

Figure 10: The COSMED K5® and Lokomat® Attachment



Data Management and Software: COSMED® provides the Metabolic Module of OMNIA, a modular software suite from COSMED®, which was installed onto a compatible Flinders University Laptop. The base unit can transfer information into this system wirelessly, or via a USB connection for further storage and analysis. From the OMNIA software participant's data can then be exported into Excel for use.

All procedures including warm-up, calibration and all tests were completed as per instructions from the COSMED K5® User Manual using COSMED® recommended and supplied items and mixed

chamber analysis. As per instructions the device requires a 20 minute warm up prior to calibrations (except for turbine calibration) or any CPET exercise test, and preferably daily calibration when used inside a non-crowded laboratory. Calibration includes the steps of:

- flowmeter calibration utilising the recommended 3L COSMED® calibration syringe,
- scrubber calibration using the provided COSMED® scrubber piece,
- reference gas calibration using the recommended gas mix of 16% O2, 5% CO2 and N2 balance and,
- room air calibration.

A2.3 P&O Clinical Movement Data by Siliconcoach

The P&O Clinical Movement Data software program (version 2.0), designed using Siliconcoach technology, is a technique or skills analysis computer software program for video analysis of human movement. The complete system for video analysis includes up to two cameras to record the participant's movement, connected to a laptop or computer with the installed software, which is used to store and analyse the video collected. Within the software program frames of the captured video can be reviewed and analysed using inbuilt tools to measure parameters such as joint angles, and speed of movement and distances (using predetermined calibration). The key components of the system loaned by Orthotics and Prosthetics South Australia for the purposes of the research are:

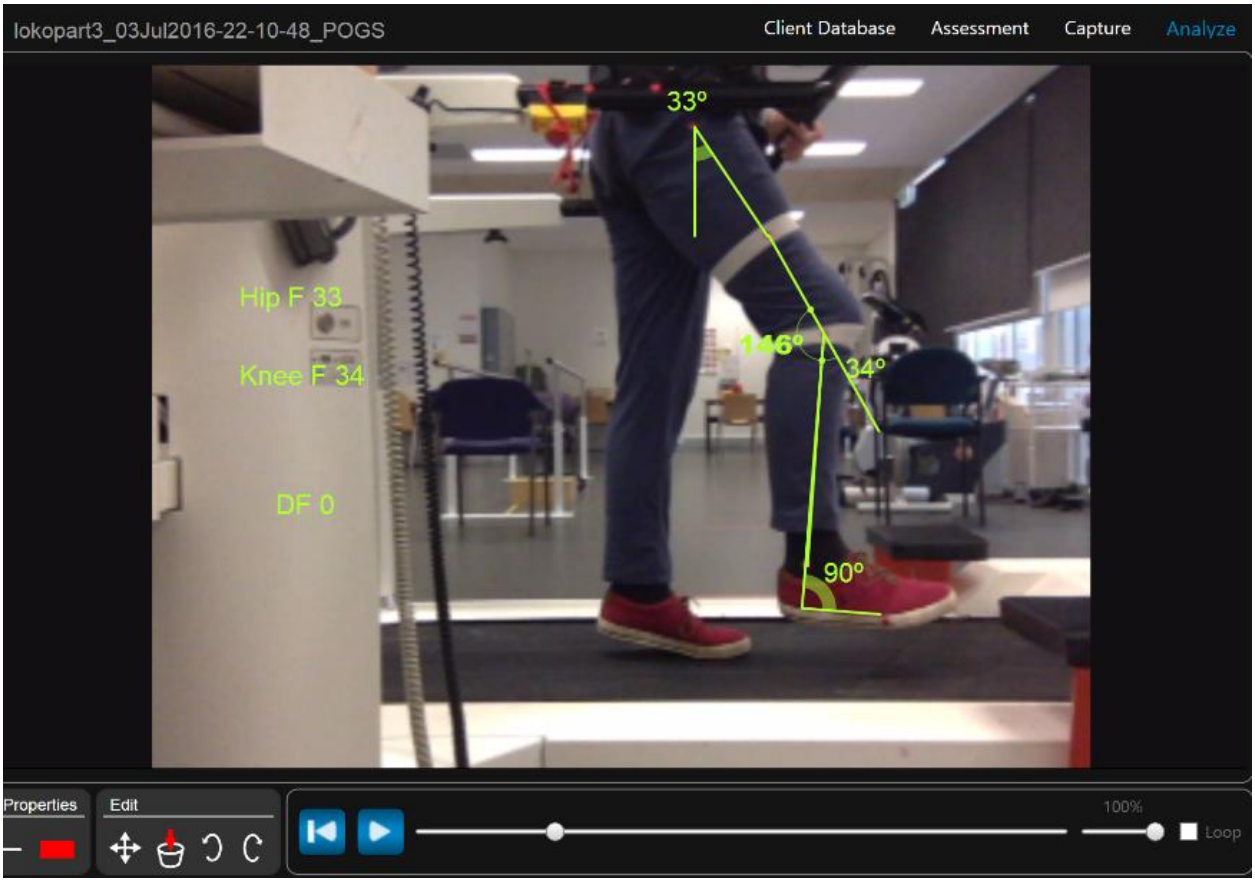
Cameras: One High Definition camcorder meeting the software system requirements (Panasonic HC-V550M, Panasonic Corporation, Australia) was set up on the lateral side of the affected lower limb at a distance allowing the pelvis to foot of the participant to be captured while on the treadmill of the Lokomat®. The camera was directly connected via cable to the computer (as below) for immediate video capture into the software program.

PC/Laptop: An Apple MacBook Pro (MacBook Pro Retina 2014, Model A152, Apple Inc, USA) was connected via cable to the video camera (above) for direct capture and storage of participant videos within the software program (below).

Software: The P&O Clinical Movement Data software package (version 2.1.0.8, P&O Data Solutions in partnership with the Tarn Group Limited, NZ) uses the Siliconcoach video capture and

analysis software technology to allow analysis of human movement. Video is analysed frame by frame with the program including tools to draw lines, measure angles and distances (via a predefined calibration from a set distance) within the video frame image (Figure 11). Other options include tracking speed of movement and overall movement trajectory. Angle tools are included within the software to measure angles between 3 points or relative to either vertical or horizontal.

Figure 11: P&O Clinical Movement Data Video Frame Example



A2.4 BORG RPE Scale

The modified CR-10 BORG scale was used with participants specifically questioned to rate their level of perceived breathing exertion as well as their level of perceived affected-leg exertion. The scale was explained to participants at consent and test ratings were completed in the fourth to fifth minute of each APF activity. The specific questions asked were: “how hard was your breathing working during that APF activity?” and “how hard was your affected-leg working in that APF activity?”

Modified Borg Scale: CR-10

0	Nothing at all
0.5	Very, very weak (just noticeable)
1	Very weak
2	Weak
3	Moderate
4	Somewhat strong
5	Strong
6	
7	Very strong
8	
9	
10	Very, very strong (almost maximal)
Maximal	

A2.5 Motivation and Enjoyment scales

A Likert scale (1 to 5) asking participants to score their level of motivation as well as enjoyment for each APF activity was printed onto plain A4 paper, explained to the participants at consent, and used to prompt participants to score in the fourth to fifth minute of each APF activity.

The specific questions were:

“How motivated were you to work hard with that APF activity?”

Lowest motivation	Low motivation	Average	Somewhat motivated	Highly motivated
1	2	3	4	5

“Please score your level of enjoyment for the APF activity.”

Lowest enjoyment	Low enjoyment	Average	Somewhat enjoyed	Highly enjoyed
1	2	3	4	5

APPENDIX 3: RESULTS

A summary of grand means and post-hoc results for study one, CV exercise on the Lokomat®, are presented in Table 9.

Table 9: Grand means and Post-Hoc Values

Stats = ANOVA		Activity Type (*p*)	Activity Order (*p*)	Session Order (*p*)
$V0_2$ (ml/kg/min)	8.0 +/- 3.8 (CI: 7.0-9.0)	0.110	0.250	0.380
MET	3.1 +/-1.3 (CI: 2.8-3.5)	0.240	0.703	0.527
BORG - D	3.5 +/- 1.7 (CI:3.1-4.0)	0.044*	0.003*	0.386
BORG - L	4.8 +/- 1.7 (CI:4.4-5.2)	0.115	0.043*	0.386
	POST-HOC	Faster >Gab 2 (*p*=0.013*) Faster to Graph (*p*=0.077) Gab 2 to Graph (*p*=0.323)	Order 1 < 2 or 3 BORG-D: 1 to 2 (*p*=0.014*) 1 to 3 (*p*=0.001*) 2 to 3 (*p*=0.544) BORG-L 1 to 2 (*p*=0.046*) 1 to 3 (*p*=0.027*) 2 to 3 (*p*=0.944)	
BWS (%)	34.6 +/- 7.6 (CI:28.8-40.4)			0.003*
GF	46.8 +/- 13.9 (CI:36.9-57.7)			0.005*
Speed	1.8 +/- 0.4 (CI: 1.5-2.1)			0.122
Stats = Friedman + Bonferroni		**Activity Type (*p*)**	**Activity Order (*p*)**	**Session Order (*p*)**
Motivation	4 (IQR: 4-5)	0.070	0.889	0.188
Enjoyment	4 (IQR: 3-5)	0.000*	0.646	0.513
	POST-HOC	Enjoy Graph Graph > Faster (*p*=0.004*) Graph > Gab 2 (*p*=0.007*) Faster to Gab 2 (*p*=1.000)		See below re post-hoc BWS and GF.

Activity Type/Activity Order: n=10 participants/56study sessions/168 APF activities, Session Order: n=9 participants/54 study sessions/162 APF activities, *= significant result (*p*=0.05), VO_2/MET/BORG=mean +/- Standard Deviation (CI=Confidence Interval 95%), Motivation/Enjoyment = median (1^{st}-3^{rd} IQR)

Regarding the analysis of APF activity type completed, Table 9 (above) demonstrates that for the post-hoc pairwise comparison for BORG-D a statistically significant difference (*p*=0.013) was found between Faster (rated higher) and Gabarello 2, but no statistically significant difference between Graph compared to either Faster or Gabarello 2 (*p*=0.077 and 0.323 respectfully). A post-hoc pairwise comparison for enjoyment revealed statistically significant greater enjoyment for the

Graph APF as compared to both Faster (p=0.004) or Gabarello 2 (p=0.007), but no significant difference between Faster and Gabarello 2 (p=1.000).

Regarding the analysis of APF activity order of completion within a study session, Table 9 (above) demonstrates that a post-hoc pairwise comparison for BORG-D revealed a statistically significant difference between the activity completed first to both that completed second (p=0.014) and third (p=0.001) but not between the activities completed second and third (p=0.544). A post-hoc pairwise comparison for BORG-L also revealed a statistically significant difference between the activity completed first to both that completed second (p=0.046) and third (p=0.027) but not between the activities completed second and third (p=0.944). For both BORG-D and BORG-L the first activity was rated lower than either the second or third completed activity.

Regarding Lokomat® parameters over the six study sessions a statistically significant difference was found for BWS (p=0.003) and GF (p=0.005) but not speed (p=0.122) (Table 9). A post-hoc pairwise comparison for BWS revealed a decrease in BWS over the six study sessions but with less significance of that difference between sessions four, five, and six (Figure 12 and Table 10). Sessions were also generally not significantly different to the immediate neighbouring or following session but were significantly different after the next subsequent session.

Figure 12: Change in BWS over Six Study Sessions

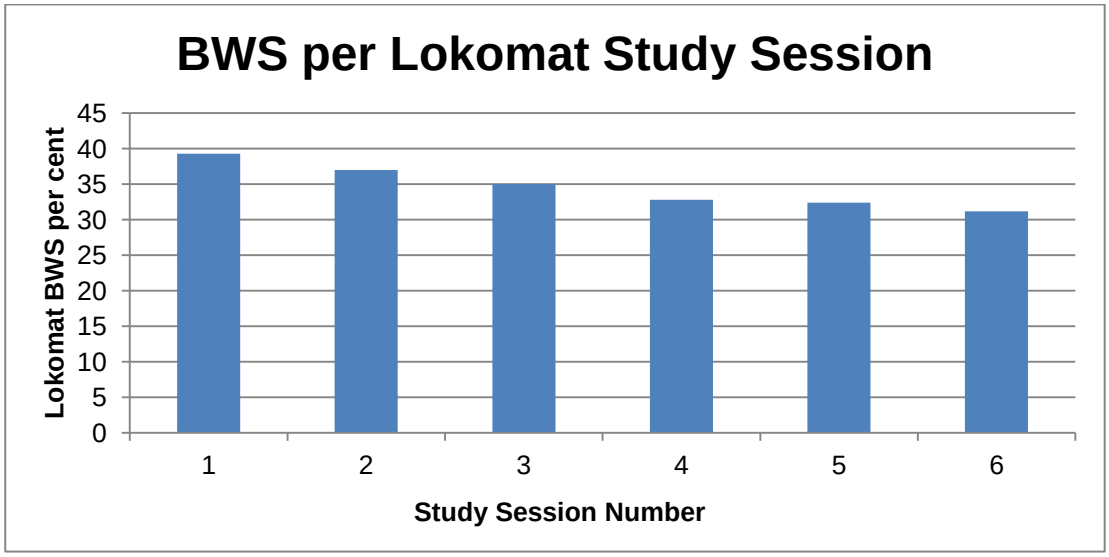


Table 10: Matrix of Statistical Significance for Body Weight Support Between Study Sessions.

	1	2	3	4	5	6
1		0.243	0.004*	0.000*	0.000*	0.000*
2	0.243		0.033*	0.019*	0.000*	0.001*
3	0.004*	0.033*		0.087	0.001*	0.010*
4	0.000*	0.019*	0.087		1.000	1.000
5	0.000*	0.000*	0.001*	1.000		0.576
6	0.000*	0.001*	0.010*	1.000	0.576	

Study sessions 1 to 6. *=significant relationship (p=0.05)

A post-hoc pairwise comparison for GF revealed a decrease in GF over the six study sessions but again with less significance between sessions four, five and six (Figure 13 and Table 11).

Figure 13: Change in GF over Six Study Sessions

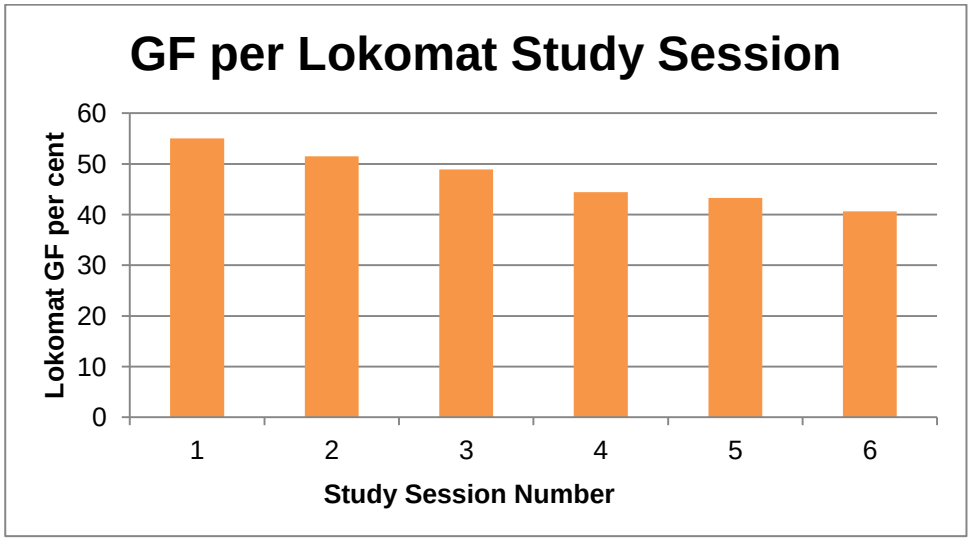


Table 11: Matrix of Statistical Significance for Guidance Force Between Study Sessions.

	1	2	3	4	5	6
1		0.130	0.034*	0.001*	0.004*	0.003*
2	0.130		0.223	0.000*	0.000*	0.001*
3	0.034*	0.223		0.001*	0.008*	0.006*
4	0.001*	0.000*	0.001*		1.000	0.348
5	0.004*	0.000*	0.008*	1.000		0.764
6	0.003*	0.001*	0.006*	0.348	0.764	

Study sessions 1 to 6. *=significant relationship (p=0.05)

Resting measures per study session are demonstrated in Table 11. VO_2, BORG-D and BORG-L at rest were not found to be statistically significantly different across the six sessions (p=0.829, p=0.845 and p=0.336 respectively).

Table 12: Comparison of Session Order – Resting VO_2, BORG

Resting	1	2	3	4	5	6	***p* value**
VO_2	2.8 +/-1.1 (1.9-3.6)	2.6 +/-0.8 (1.9-3.2)	2.4+/-1.0 (1.6-3.2)	2.6 +/-0.7 (2.1-3.1)	2.8 +/-0.9 (2.1-3.5)	2.9 +/-1.2 (2.0-3.8)	0.829
BORG-D	1.4 +/-1.1 (0.5-2.3)	1.9 +/-1.2 (1.1-2.8)	1.8 +/-1.6 (0.5-3.0)	1.6 +/-1.1 (0.7-2.4)	1.6 +/-1.2 (0.7-2.5)	1.6 +/-1.5 (0.5-2.7)	0.845
BORG-L	0.6 +/-0.9 (0.0-1.3)	0.9 +/-1.3 (0.1-2.0)	1.3 +/-1.3 (0.3-2.2)	0.5 +/-0.9 (0.2-1.2)	0.6 +/-1.0 (0.2-1.4)	0.8 +/-0.8 (0.2-1.4)	0.336

n=56 sessions/10 participants, significance (p=0.05), VO_2/BORG= mean +/- Standard Deviation (Confidence Interval = 95%),

Weak correlations were found between VO_2 and either BORG-dyspnoea or BORG-leg as detailed in Table 13.

Table 13: Correlation VO_2 and BORG

	VO_2	BORG-D	BORG-L
VO_2	1	0.477	0.328
BORG-D	0.477	1	0.436
BORG-L	0.328	0.436*	1

n=10participants/168 data points

APPENDIX 4: DATA COLLECTION SHEET

Data Collection Record: **Participant No:…….**

Age (years)		
Gender (M/F)	Male	Female
Date Stroke		
Date admit rehab		
Date Start Lokomat – RGH IP		
Date consent to study		
Time since stroke		
Stroke Type	Ischaemic	Haemorrhagic
Hemi side	Left	Right
Height (cm)		
Weight (kg)		
BMI		
FAC		

Appendix—Description of Functional Ambulation Category (FAC)

FAC	Ambulation Description	Definition
0	Nonfunctional ambulation	Subject cannot ambulate, ambulates in parallel bars only, or requires supervision or physical assistance from more than one person to ambulate safely outside of parallel bars
1	Ambulator-Dependent for Physical Assistance Level II	Subject requires manual contacts of no more than one person during ambulation on level surfaces to prevent falling. Manual contacts are continuous and necessary to support body weight as well as maintain balance and/or assist coordination
2	Ambulator-Dependent for Physical Assistance Level I	Subject requires manual contact of no more than one person during ambulation on level surfaces to prevent falling. Manual contact consists of continuous or intermittent light touch to assist balance or coordination
3	Ambulator-Dependent for Supervision	Subject can physically ambulate on level surfaces without manual contact of another person but for safety requires standby guarding on no more than one person because of poor judgment, questionable cardiac status, or the need for verbal cuing to complete the task.
4	Ambulator-Independent Level Surfaces only	Subject can ambulate independently on level surfaces but requires supervision or physical assistance to negotiate any of the following: stairs, inclines, or non-level surfaces.
5	Ambulator-Independent	Subject can ambulate independently on nonlevel and level surfaces, stairs, and inclines.

Session 1:

Date:	**APF**	**K5 timer start**	**K5 4 min**	**K5 timer end**	**BWS Kg/%**	**GF %**	**Speed kph**	**BORG D**	**BORG L**	**Mot**	**Enj**	**VO_2**	**MET**
Rest													
Warm up													
Activity 1													
Activity 2													
Activity 3													

Session 2:

Date:	APF	K5 timer start	K5 4 min	K5 timer end	BWS Kg/%	GF %	Speed kph	BORG D	BORG L	Mot	Enj	VO_2	MET
Rest													
Warm up													
Activity 1													
Activity 2													
Activity 3													

Session 3:

Date:	APF	K5 timer start	K5 4 min	K5 timer end	BWS Kg/%	GF %	Speed kph	BORG D	BORG L	Mot	Enj	VO_2	MET
Rest													
Warm up													
Activity 1													
Activity 2													
Activity 3													

Session 4:

Date:	APF	K5 timer start	K5 4 min	K5 timer end	BWS Kg/%	GF %	Speed kph	BORG D	BORG L	Mot	Enj	VO_2	MET
Rest													
Warm up													
Activity 1													
Activity 2													
Activity 3													

Session 5:

Date:	APF	K5 timer start	K5 4 min	K5 timer end	BWS Kg/%	GF %	Speed kph	BORG D	BORG L	Mot	Enj	VO_2	MET
Rest													
Warm up													
Activity 1													
Activity 2													
Activity 3													

Session 6:

Date:	APF	K5 timer start	K5 4 min	K5 timer end	BWS Kg/%	GF %	Speed kph	BORG Dysp	BORG Leg	Mot	Enj	VO_2	MET
Rest													
Warm up													
Activity 1													
Activity 2													
Activity 3													

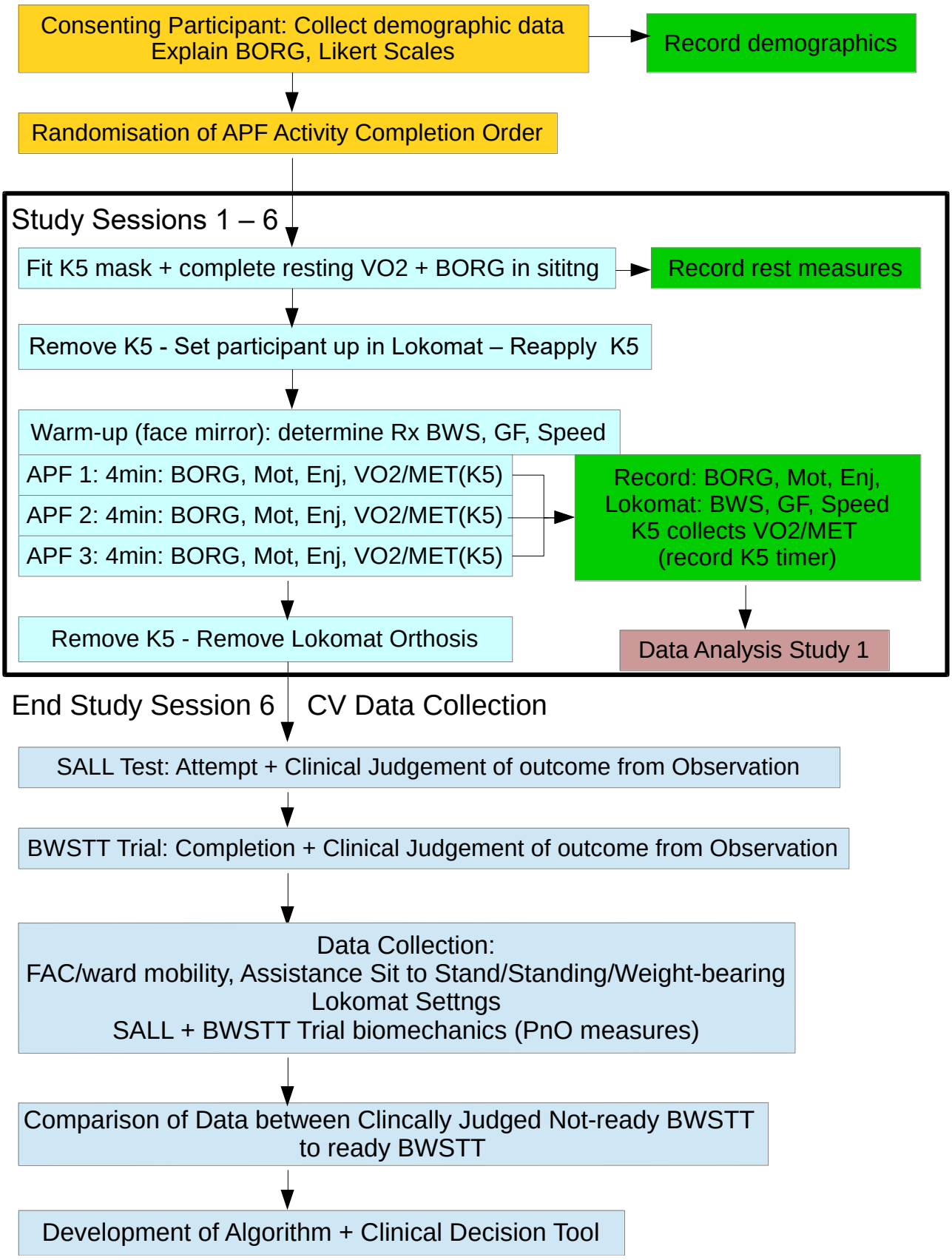
Ready BWSTT

Date:					
Able attempt SALL	Y	N	**Attempt BWSTT**	Y	N
Video collected	Y	N	**Video collected**	Y	N

Clinical Judgement SALL / BWSTT - reasons	
No Lokomat sessions Pre-study session 1	
No Lokomat sessions in study	6
No Lokomat sessions pre-Ready BWSTT	
No Lokomat / BWSTT session pre DC	
FAC/ward mobility Study Session 6	
Sit to stand/stand balance/WB Study session 6	

APPENDIX 5: PARTICIPANT FLOW

Figure 14: Study Participant Flow



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