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Mémoire de Maîtrise en médecine

Analysis of the evolution of quality of life of patients with spinal cord injury throughout the clinical trial with spinal epidural electrical stimulation (EES) in combination with Robot-assisted neurorehabilitation (STIMO).

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Abstract

Main Idea:
Analysis of the evolution of quality of life (QoL) of patients with spinal cord injury (SCI) throughout the clinical trial STImulation of Movement Overground (STIMO) with spinal epidural electrical stimulation (EES) in combination with Robot-assisted neurorehabilitation. ClinicalTrials.gov Identifier: NCT02936453.

Introduction:
As already cited in the STIMO protocol, SCI patients usually have a diminished QoL.
This new therapy, by EES in combination with a robot-assisted neurorehabilitation, being tested for the very first time in humans will enhance the ability to stand and walk which has an impact on these patients' day to day living as the increased independence in activities of daily living is a key point in the QoL index. The study only takes into consideration objective test values obtained in the walking laboratory, and excludes the global, subjective changes in day to day living. An evaluation pertaining specifically to patients with spinal cord injury, more precise and detailed than at STIMO study initiation, therefore seems to be a significant addition.

Objective:
To put in place a more detailed and effective system for the evaluation of QoL of STIMO trial patients. To enable a more in-depth analysis that goes further than the SF-36 questionnaire that is used in the original protocol.

Method:
A subjective, specific and internationally recognized questionnaire, the WHOQOL-Bref was added to the study at the following timepoints: pre-rehabilitation, intermediate, post-rehabilitation, 3-months extension, 6-month extension. Analysis of functional independence with the SCIM III at pre-rehab, intermediate, post-rehab and both extensions. Analysis of the evolution of HRQoL with the SF-36 at pre-implantations, pre-rehabilitation, post-rehabilitation and 6-months extension.

Expected results:
Concurring with the expected results of the STIMO trial, we hope to obtain an improvement in the patients' QoL. We hypothesize that there will be a correlation between the objective values obtained in the walking lab of functional independence evaluated with the SCIM III questionnaire and of health-related QoL obtained through the SF-36 questionnaire, and the subjective values in the patients' everyday environment evaluated with the WHOQOL-Bref survey.

Added value:
This analysis will add a more thorough and detailed dimension to the evaluation of the QoL, including more parameters than just the ability to move and walk during the experiment. It will take into consideration the psychological, social, environmental point of view of the patient. In the end, these values that influence the patients' day to day living are significant for the end results of the trial.

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Introduction

Spinal cord injury (SCI) is a life-changing damage to the spinal cord that was considered a terminal condition in previous generations. In recent years, however, mostly in high-income countries, medical advancement such as better first response care, rehabilitation treatments and assistive devices, has made its mortality rates stabilize and slowly diminish. (1,2) More SCI patients are able to survive the acute phase directly following the trauma and have to adapt to a chronic stage of SCI which necessitates a more personal, social, and environmental adjustment. Note that all these above stated items have an important influence on an individual's quality of life (QoL).

Spinal Cord Injury Epidemiology

SCI data in literature is sparse making worldwide prevalence, incidence and demographics studies difficult to evaluate. (2,3) Spinal cord injuries are separated into two categories: nontraumatic spinal cord injury (NTSCI) which is SCI that is not caused by an external trauma but rather by internal causes such as cancer, infection, ischemia, inflammatory or congenital disease, or metabolic disorders for instance(4) and traumatic spinal cord injury (TSCI). Current literature mostly concentrates on TSCI making NTSCI data hard to find. Furthermore, the STIMO study's patients are all TSCI individuals. We will, therefore, concentrate on TSCI demographics. Prevalence is defined as the number of people in the population living with SCI at a given time point and is influenced by the existing risk factors and time span of a condition. A proper evaluation of SCI prevalence would allow the further development of SCI prevention. In a 2013 WHO's analysis, traumatic spinal cord injury (TSCI) worldwide prevalence ranged from 280 per million population in Finland to 1298 per million in Canada. [see table 1]. These excessive variations are probably due to differences in methodology according to the study along with variation in prevention and safety from one country to another.

Table 1. Prevalence of TSCI. Source: (2).

Country	Locality	Year of estimate	Study design and reference population	Paediatric /adult SCI	Prevalence per million population
Islamic Republic of Iran	Tehran	2008	Prospective, cross-sectional, national registry	Adult, paediatric	440
Finland	Käpylä Rehabilitation Centre, Helsinki; Helsinki University Central Hospital, Helsinki	1999	Retrospective, registry of hospital data	Adult, paediatric	280
Norway	Hordaland and Sogn og Fjordane counties	2002	Retrospective, longitudinal/ cohort using hospital data	Adult, paediatric	365
Iceland	Landspitali University Hospital, Reykjavik	2009	Retrospective, longitudinal/ cohort using hospital data	Adult, paediatric	526
Canada	Nationwide	2010	Retrospective, cross-sectional, national registry, modelling study	Adult, paediatric	1298
Australia	Nationwide	1997	Retrospective, national registry, modelling study	Adult	681

Sources (1–6).

Figure 1. Global variation in country-level estimates of annual incidence of TSCI. Source: (2).
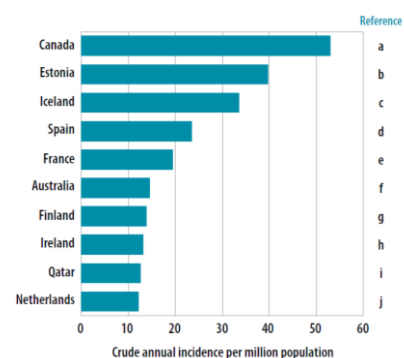

Incidence corresponds to the number of people who have suffered a SCI in a given population over a given period of time, generally per year. Global SCI incidence seems easier to estimate than prevalence at approximately 40 to 80 new cases per million population per year. This global incidence is based on country-level incidence studies from all causes of SCI with similar and accepted methodologies. This means 250 000 to 500 000 SCIs occur every year. More specifically, TSCI incidence rates vary from 13 per million population in the Netherlands to 53 cases per million population in Canada.(2) [see Figure 1]. A few trends can be perceived from incidence analysis in these different countries. Incidence rates for male adult TSCI are almost

double the incidence rate of female adults worldwide.(1–3) In a few studies, the ratio is even higher; in Ireland and Brazil for instance the ratio is >5:1. (5,6) Also, two main time peaks in age are seen for TSCI : young adults (16 to 30 years old) probably due to a higher chance of work related or road accidents and the elderly (> 60 years old) due to a higher chance of falls. If we take the United States as an example, falls in individuals aged 65 years or older in 1997-2000 represented 28% of SCI whereas in 2010-2012 represents 66%. (7)
The expansion of human activity over the years plays an important role in the increase in incidence and prevalence of SCI in the population.(1)

The three most common etiologies of TSCI are as follows and in this order of frequency: road traffic accidents, falls and violence (self-harm included). These causes are more or less frequent depending on the country. [see figure 2] Falls are becoming the number one cause in the aging-population which explains the second age peak seen in incidence rates (> 60 years old). Although falls are quickly equalizing with road traffic accidents in developed countries, motor vehicle accidents are still the main cause of TSCI in non-developed countries. (1,3)

Figure 2. Distribution of TSCI by WHO region. Source : (2).
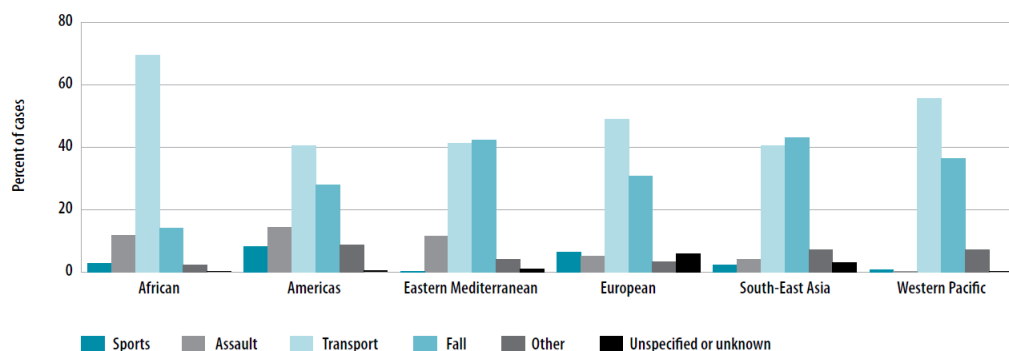
Note: The numbers of countries providing data for regional summary are as follows: African 3 countries; Americas 4; Eastern Mediterranean 5; European 13; South-East Asia 3; and Western Pacific 3 countries.
Sources: African – (*38–45*); Americas – (*12, 30, 32, 35, 46–52*); Eastern Mediterranean – (*4, 53–56*); European – (*2, 3, 9, 13, 17, 18, 20, 26, 57–67*); South-East Asia – (*68–72*); Western Pacific – (*16, 21, 22, 34, 73–80*).


In SCI individuals, the risk of mortality depends on the level and severity of the injury. Individuals with higher and complete lesions will have a lesser chance of survival. (2) Life expectancy of individuals with SCI firmly depends on improvement in SCI diagnosis, emergency care units, general clinical care and development of better rehabilitation techniques. (1) It can be seen in demographics analysis that individuals with SCI in high-income countries who can afford such care have a decreased mortality risk from secondary health conditions. The main causes of death in high-income countries for the spinal cord injured population are respiratory diseases like pneumonia and influenza and circulatory system diseases, which are all problems similar to those of individuals without SCI and not secondary to SCI. Still, individuals with SCI worldwide die before and more frequently than the general population.(1)
The cost of SCI goes hand in hand with life expectancy and mortality. Parallelly, it depends on the level and severity of the injury, the timeline of treatment needed (the length of time in the hospital and the onset of secondary health conditions (SHCs)), direct medical costs for assistive devices for instance and indirect costs linked to individual productivity loss. A patient with a higher lesion (tetraplegia), complete lesion, with more SHCs and who is less productive for society will cost more.(2)

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SCI Epidemiology in Switzerland

In Switzerland, the Swiss Spinal Cord Injury (SwiSCI) Cohort study is the main platform used for estimating TSCI demographic evolution. The data is representative of the Swiss population as a whole and is given following demographic and characteristics specific to SCIs. In this data, the conclusions drawn are similar to worldwide incidence deductions. Out of 932 cases, 239 were female versus 693 males putting the female-male ratio at 1:3. This result is similar to the average global ratio which is superior to or equal to 1:2. Just like in most countries, there are less cases of complete lesion than cases of incomplete lesion and the leading causes of TSCI are falls (aging-population) and sports or leisure-related injuries for both males and females. The average age for TSCI is 48.0 years old. In Switzerland from 2005 to 2012, the total annual incidence rate for TSCI was 18.0 per million which is slightly higher than global overall annual incidence rate but intermediate when compared to other countries. [see figure 3]. One difference with general global demographics is that paraplegia (affecting inferior limbs) is more common than tetraplegia (affecting all four limbs) in Switzerland.(8)

Figure 3. European estimates of annual TSCI incidence per million population. Comparison of reported annual incidence rates per million population for European countries with similar methodology. Source:(8).
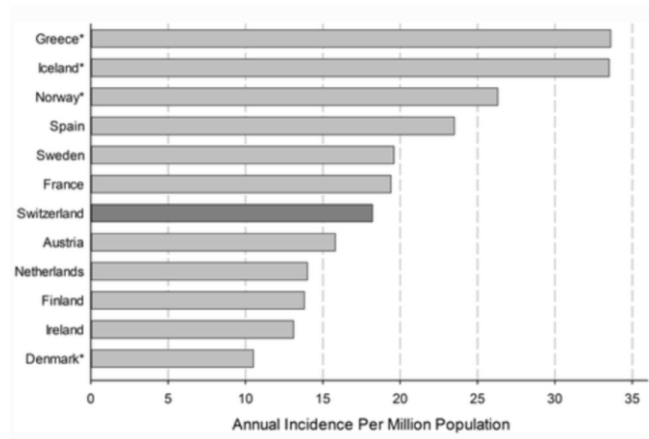

QoL in SCI patients

Following a SCI, the body fights to recover the functions that have been lost. Many severe impairments in bladder, bowel, cardiac, respiratory, sensory and sexual function occur. Be it locomotion, sphincter control, sexual dysfunction, autonomic dysfunction, all these secondary complications, acute and chronic, have an important effect on the individual's QoL. The patient struggles with day to day activities and needs time for adjustment and a coping process. Not surprisingly, people with SCI tend to report a lower QoL than non-disabled individuals.(9)

Defining QoL in SCI is not easy. Many different aspects must be taken into consideration. One definition given by the WHO is: "an individual's perceptions of their position in life in the context of the culture and the value systems in which they live, and in relation to their goals, expectations, standards and concerns".(10) Other studies define it as ; "the sum total of the cognitive and emotional reactions that people experience when they compare what they have and do in life with their aspirations, needs, and other expectations" (11). Throughout literature, one precise and repeated definition is hard to find. This existing lack of consensus makes it difficult to find harmony on how to measure QoL and follow its evolution over time. The QoL concept is one of the most controversial medical, rehabilitative, social and psychological constructs dealt with in clinical

research.(11) It can include the person's physical health and level of functioning but also a person's psychological well-being, happiness, the individual's current life situation and satisfaction, social participation and response to the environment. (12,13) Individuals each value different aspects of life. QoL seems to be an extremely subjective experience likely influenced by cognitive factors.(9,13) Only quantifying it through objective measurements, as it is frequently done in literature, doesn't seem judicious.(14) Frequently, an inconsistency is seen between clinical measures and the patient's individual assessment of health.(15) A distinction must be stressed between objective and subjective QoL which turn out to be two different approaches to QoL. One is considered a rather medical/somatic approach and the second, a rather psychological approach. (16) What complicates the concept of QoL is that both these approaches interact one with the other. As seen in Figure 4 of Tramonti et al 2014 below (12), health-related QoL (HRQoL) cannot be interpreted without functional statuses allowing evaluation of physical function but individualized QoL and evaluation of mental health must also be included. Correlations between these elements must be seen as a continuum. (12) As stated in Megari et al 2013, "in sum, QoL is inherently a dynamic, multilevel and complex concept, reflecting objective, subjective, macro societal, and micro individual, positive and negative influences which interact."

Figure 4. Pattern of associations among different measures of QoL and functional status. Source:(12). (Here replace SEIQoL-DW not used in our study with the WHOQOL-Bref.)
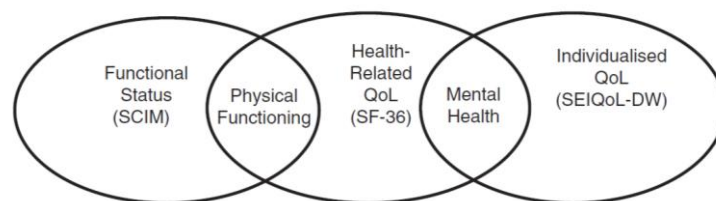
Objective QoL
The most frequently used definition of QoL, (the one usually referred to in clinical trials when QoL is not clearly defined) is objective Qol, also referred to in literature as HRQoL or "QoL as utility" following the Dijkers model of QoL.(11) HRQoL can be defined as course of life altered by "impairments, functional states, perceptions and social opportunities". Often, researchers divide HRQoL into specific life domains: physical, psychological and social functioning in regards to disease or treatment. This means HRQoL refers to the extent to which illness, injury, or treatment can influence the individual's experience of life. (12,13,17) Indeed, many SCI research uses this 'definition' of QoL when evaluating it. HRQoL measurements lack the overall sensitivity to reflect change and note a difference in evolution between people with SCI. Interindividual differences in perception and expectations are not addressed in SCI research. In evaluating new technology, treatment and rehabilitative methods, it seems important to incorporate measures of QoL that take into consideration the significance each such domain has for the SCI individual. (11–13,18)

Subjective QoL
Subjective Qol, frequently referred to as individual QoL "QoL as subjective well-being"(11) and finally "patient centered evaluation of Qol"(12), is a personal evaluation of life satisfaction based on specific domains that are considered more important to the individual. What stands out in subjective QoL is known as "domain importance". The usual domains that contribute to overall QoL as seen above included in HRQoL (physical, psychological and social functioning, material well-being…) have a different inter-individual value which must be assessed. Evolution in satisfaction in a domain that scores extremely high on the individual's scale of domain importance will have much greater impact than improved satisfaction within a lesser domain.(12,18–

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20) The psychological domain, mentioned above, is especially patient centered. Self-control, self-worth, self-esteem, self-purpose and hope, optimism along with low posttraumatic cognition and high affects are all positive psychological factors considered to be determinant in QoL literature.(21) In recent research, these personal factors stood out to explain a significant amount of discrepancy in life satisfaction. (12,22) In SCI QoL measurements, subjective domain importance must imperatively be taken into consideration to avoid giving equal importance to evolution of specific domains. However, the word 'subjective' in research is usually negatively connotated as non-objectifiable and could be more complicated to evaluate.(13)

Secondary Health Conditions
A secondary health condition (SHC) is defined by the Institute of Medicine as : "a condition that is causally related to a disabling condition (that is, occurs as the result of a primary disabling condition and that can either be a pathology, an impairment, a functional limitation or an additional disability)". (23) In SCI, SHCs are extremely frequent and considered key determinants in the evolution of the disability, mortality, life expectancy and well-being.(24) 95% of SCI individuals experience one or more of these conditions.(25,26) Six of these SHCs stand out regarding frequency (reported prevalence of over 50%) and effect on the SCI individuals life : spasticity, chronic pain, bladder and bowel problems, sexual dysfunction and sleep. (14–17) [see figure 5.a.] These findings are in agreement with results from SwiSCI cohort in Switzerland. As seen in Brinkhof et al 2016's figure [see figure 5.b.], in Switzerland, sexual dysfunction, sleep and spasticity are three chief SHCs that patients report as significant or chronic and more importantly that report that aren't receiving treatment for.(24) Both quadriplegics and paraplegics rate these conditions as important concerns and furthermore, say they have difficulty dealing with them.(9)
Constant or daily pain that lasts more than three months is termed chronic pain. Up to 80% of individuals with SCI experience chronic pain which mainly includes musculoskeletal, neuropathic and visceral pain.(31,32) Many studies draw a parallel between chronic pain and lower psychological functioning along with diminished QoL. (31–34)
Spasticity is experienced by 70% of all SCI individuals following the first year after the injury. It refers to muscles spasms and clonus along with a rise in muscle tone and exaggerated tendon reflexes. (34,35) Slight spasticity can be advantageous to SCI individuals but the severe spasticity usually experienced causes pain and decreases QoL.(36,37) Spasticity is also related to sleep problems, fatigue and bladder dysfunction, all elements that SCI individuals are very effected by on a daily basis.(38)
Bladder problems in SCI include incontinence, bladder or kidney stones, kidney malfunction, urine leakage or urine backup and kidney or bladder infections. Bowel disorder in SCI is widely due to neurogenic bowel. This leads to diarrhea or constipation, 'accidents', and visceral pain. (24) These bowel and bladder dysfunctions severely influence many aspects of QoL, especially social and psychological. For instance, on a social viewpoint, reintegrating society and maintaining relationships is made more difficult when controlling bowel movements and avoiding urine leakage are major concerns.
Sexual health is defined as: "a state of physical, emotional, mental, and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction, or infirmity".(69) For instance, decreased sensation, difficulty in movement and problems with bowel and bladder control in patients with SCI can lead to dissatisfaction with sexual functions. Sexual function is the most frequent problem that isn't treated or enough evoked by health care professionals according to SCI individuals. (24) Individuals with paraplegia rate regaining sexual function as their highest priority to improve QoL. (9)
In many studies, neurologic disorders have proven to significantly compromise sleep. In SCI, sleep disorders seem to have an important effect on QoL. Disrupted sleep leads to increased pain, spasticity and mostly fatigue which has an important psychological effect on SCI individuals. (39)

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Figure 5.a. Prevalence of reported health condition problems and existing diagnoses. 95% CI: 95% interval. 5.b. Rates of reporting non-treatment for health conditions (HCs) of significant or chronic severity (SCI-SCS, level 3, Appendix 1). Both from source:(24).

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a.

b.
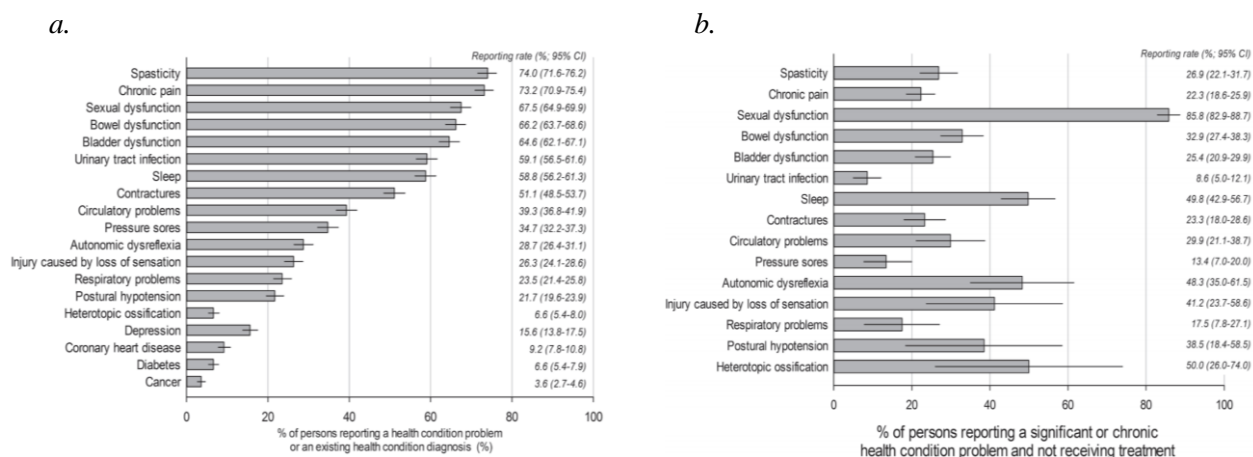
Socially, psychologically, physically and financially, these 6 SHCs diminish SCI individuals' life satisfaction and emotional well-being. (24) QoL of SCI patients is highly influenced by the manifestation of these health conditions. These must be included in defining it. (9)

Other factors also influence QoL in SCI patients : age at injury, time since injury, level of lesion, low functional independence, social support, financial status. (34) Most of these factors are stable and constant meaning they do not influence evolution of QoL with time. Regaining some movement or function can lead to increased independence and is linked to increased QoL of individuals with SCI. (24,40) SHC have a higher impact on SCI individuals subjective QoL. In Rivers et al's 2018 study, health conditions had a greater effect than functional independence. (30)

Minimal clinically meaningful difference (MCID)

Taking into consideration all of the aspects that make up the complex concept of QoL, broad clinical evaluation is far from simple. (11) In literature, the minimal clinically meaningful difference refers to the smallest variation in a score considered clinically important. This means "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management."(41,42) When this concept is applied to QoL measurements, an absolute minimum is risky to identify and can easily oversimplify the measurement. MCID in QoL are many times clinically relevant but statistically irrelevant. In a study by Barber BL et al, it was shown that patients that perceived minor improvements in their asthma considered these minimal changes important, but being too small, were not reflected.(43) In QoL survey's, MCID's are not definable and not used. Researchers are faced with two main problems when defining a MCID for QoL measurements. The direction of the evolution can have an effect on the meaning of the change. A positive increase could have a different impact than an equal value negative decrease. The meaning of change depends on the individual patient's baseline of perceived health. A patient with more room for change will show a more important evolution be it negative or positive evolution. The evolution of patients closer to a high score on the QoL evaluation would be more difficult to identify. This is known as "celling (high scores) or floor effects(low scores)"(42).

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Adaptation and response shift

Initially, directly following a spinal cord injury, overall QoL drops due to the drastic reduction of satisfaction in important life domains and the feeling of loss of control over the individual's life caused by the debilitating injury.(44) This drop will depend on the severity of domain affected and domain importance. Time in SCI and most of all in QoL for SCI individuals is essential.(45) SCI patients go through an initial acute phase from the time of the injury to approximately 1-year post injury. In this phase, neuro-rehabilitation is essential to allow recovery of motor function. Adaptation to the new situation usually starts taking place.(44) With time, the SCI is considered chronic. The patient reaches a limit and motor progression is more difficult. SHCs become more predominant in regard to QoL. SCI becomes a chronic condition with heavy physical and emotional costs. Individuals with SCI experience its consequences on a long period of time driving them to adapt and adjust to this condition. Individuals with lower QoL constantly seek to gain QoL points and reach their desired QoL level.(12,46) Adaptation is vital to living with SCI and coping mechanisms are a major focus in current rehabilitation.(47) This accommodation to a chronic condition is known as "response shift" and plays an important role in the evaluation of subjective QoL.(15) Response shift is defined in literature as : "a change in the meaning of one's self evaluation of a target construct as a result of a change in the respondent's internal standards of measurement or scale recalibration".(13) Individuals will repeatedly experience secondary health conditions (SHCs) with time, adapt to these SHCs which means these SHC won't impact their self-evaluation of QoL as much as they would have in a more acute situation. Response shift seems to be a good explanation as to why life satisfaction in patients who have lived longer with SCI tends to be effected less negatively by the occurrence of health conditions. (28) Frequently observed positive factors to psychological adjustment in SCI are age and time since injury.(48) Not all measures are affected equally by response shift. Less the concept of the measurement is concrete and objective, more it will be affected by response shift. In evaluating functional independence, response shift will not have an effect. The individual can or cannot walk 500m. His or her perception is not taken into consideration. As seen previously, the evaluation of QoL is subjective and it's definition variable throughout literature making it very prone to response shift.(13,49) To obtain a valid and sensitive evaluation of evolution of QoL over time, the effect of response shift should be taken into consideration. (15)

Once an individual has undergone response shift, meaning he or she has created coping strategies and adapted to a situation, changing the baseline reached is difficult. Positive events and evolution are harder to bring to light in the evaluation of QoL. Once established in chronic injury, QoL is hard to change. Chronic SCI individuals' QoL with time tend to reach similar values than general population's QoL. (50)

Introduction to the STIMO study

In recent literature, only few clinical trials or rehabilitative techniques have shown advancement in recovering the ability to walk or stand after SCI. Electrical stimulation of muscles, epidural and intraspinal electrical spinal cord stimulation has been tested in order to assist SCI patients in verticalization and getting back on their feet.(1,51,52) Locomotion in SCI patients is noticeably eased by epidural electrical stimulation. These stimulations help induce plastic changes in sensorimotor circuits below injury directly affecting stepping pattern over time. Courtine et al. was able to show that the combination of lumbo-sacral pharmacological and electrical spinal stimulation after a week in rodents that had undergone a complete spinal cord lesion, transformed their medullar pathways from non-functional to highly functional. Stimulation in combination with intensive rehabilitation training permitted rodents to recover full 'voluntary stepping-like' hindlimb locomotion with assistance for balance. (53) In humans, reorganization of sensorimotor circuits happens spontaneously following incomplete spinal cord injury and is highly influenced by neurorehabilitation. This reorganization usually reaches an unsurpassable threshold. The STIMO study or Efficacy of Spinal Epidural Electrical Stimulation (EES) in combination with Robot-assisted neurorehabilitation in individuals with Spinal Cord Injury Study, a safety and feasibility study, was developed to facilitate recovery of locomotion in chronic

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incomplete spinal cord injured patients. Combined with a body-weight support system that enables over-ground walking for motor training, the stimulation improves locomotion when activated but also in the long run without activation.(54) Recently, a proof-of concept has been validated in three male individuals with chronic cervical SCI leading to sever lower limb deficit or complete paralysis. Indeed, this combined technology has improved and restored standing and walking capacities in these patients. (55) Functional improvement facilitates these patient's ability to get around and ease day to day activities that had been compromised by loss of motor function. It seems important to evaluate these patient's QoL over the time of the study in order to see how significant the effect of this therapy can be. Could the improvements in motor function demonstrated in STIMO be sufficient to have a quantifiable and significant impact on these individuals' QoL?

Hypothesis

The improvement of motor function gained through the STIMO trial will affect SCI patient's QoL.

Study design

The STIMO study is a monocentric prospective pilot study divided into three stages [as seen in Figure 6]. The main study during rehabilitation takes place in the STIMO Gait laboratory at the Centre Hospitalier Universitaire Vaudois (CHUV) with assessment at the Balgrist University Hospital Spinal Cord Injury Center and lasts about 5 to 6 months for each single case. An optional study extension with home use of the devices for neurorehabilitative training with EES lasts a minimum 3-year period.

Figure 6. STIMO study timeline. Source: (55).
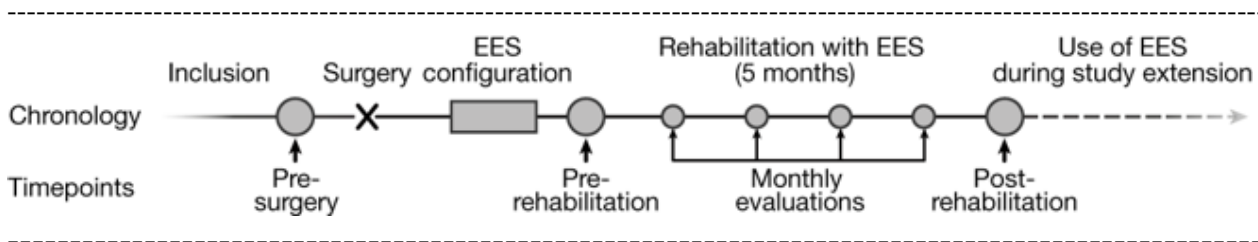
Test subjects

This QoL study includes 3 SCI subjects, all males included in the STIMO study. The STIMO study will enroll N=8 subjects with chronic (>12 months after date of injury), incomplete SCI. Inclusion criteria are: age 18 to 65 years old (women or men); incomplete SCI graded as American Spinal Injury Association (ASIA) Impairment Scale (AIS) C and D, level of lesion T10 or above with preservation of conus function, intact distance between the cone and the lesion must be at least 60mm; focal spinal cord disorder caused by either trauma or epidural, subdural or intramedullary bleeding; minimum 12 months post-injury, completed in-patient rehabilitation program (must be aware of functional limitations); able to stand with walker or two crutches; adequate care-giver support and access to appropriate medical care in individuals' home community. The individual must be clinically stable (the individual has attained a plateau at which no further functional improvements can be reached) and most importantly psychologically ready to undergo an intensive neurorehabilitative training (STIMO protocol version 1.2). Exclusion criteria include : motor functions limited by additional disorders (systemic malignant, cardiovascular, peripheral nerve disorders); history of significant autonomic dysreflexia; brain damage; epilepsy; patients with baclofen pumps, active implanted cardiac device, with an indication to diathermy, who would require MRI, with increased risk of defibrillation, with restricting lower limb movements from severe joint contractures, with hematological disorders, who are participating in

another locomotor training study, with known or suspected non-compliance, drug or alcohol abuse; women who are pregnant; congenital or acquired lower limb abnormalities; non-traumatic spinal cord lesion; patient could be limited in investigator's opinion; patients whose life expectancy is less than 12 months.

Method

In the original STIMO protocol (version 1.2), the SF-36 survey was the only questionnaire dedicated to evaluating QoL throughout the study as a means to evaluate the healthcare being provided. This questionnaire is referred to as a generic measurement of the state of health by assessing eight health domains: limitations in physical functioning (PF), limitations of role due to physical health (RP), bodily pain (BP), general health (GH), vitality and fatigue (VT), limitations of role due to emotional problems (RE), social functioning (SF), and mental health or emotional well-being (MH). These eight domains can be divided into two entities: the physical component score (PCS) and the mental component score (MCS). The PCS includes: high scores of PF, RP, BP and GH and low scores on the RE and MH. Inversely, the MCS is in relation with high scores on the MH, RE, SF and VT scales and low scores of the PF and RP scales. The questions are scored on a 1 to 6 scale depending on the question. Each score obtained must first be recoded using the values as seen in table 2.A. The sub-scales are created by averaging the question scores as seen in table 2.B. This makes up what is referred to as the transformed scores for each sub-scale. For the general population, the normative value of the mean score is 50 for each of these eight domains with a normative value of the standard deviation at 10. (SF-36 scoring instruction RAND); (56,57)

Table 2. Scoring instructions to obtain the SF-36 transformed scores. A. Recoded values depending on original response for each the item. B. Items to average to obtain each sub-scale score. Source: SF-36 scoring instructions RAND.

A.

Item number	1,2,20,22,34,36		3,4,5,6,7,8,9,10,11,12		13,14,15,16,17,18,19		21,23,26,27,30		24,25,28,29,31		32,33,35	
	Original response	Recoded value	Original response	Recoded value	Original response	Recoded value	Original response	Recoded value	Original response	Recoded value	Original response	Recoded value
	1	100	1	0	1	0	1	100	1	0	1	0
	2	75	2	50	2	100	2	80	2	20	2	25
	3	50	3	100			3	60	3	40	3	50
	4	25					4	40	4	60	4	75
	5	0					5	20	5	80	5	100
							6	0	6	100		

B.

Health concept	Number of items	Items to average
PF	10	3,4,5,6,7,8,9,10,11,12
RP	4	13,14,15,16
RE	3	17,18,19
VT	4	23,27,29,31
MH	5	24,25,26,28,30
SF	2	20,32
BP	2	21,22
GH	5	1,33,34,35,36

In terms of validity in the SCI population, the SF-36 is frequently used.(56) A few issues do however exist in reference to SCI individuals: three questions that refer to walking and climbing stairs are not applicable for patients who may use a wheelchair to move. Floor effects or compressed scale ranges could be more frequent in using this survey in the SCI population because it doesn't distinguish between the general population and the disabled population. (58)

The first addition to the STIMO study questionnaires (protocol version 1.10) was to the WHOQOL-Bref (World Health Organization Quality of Life- Bref) questionnaire. This allowed a more sensitive and subjective QoL analysis as well as more specific to SCI that was not available to us with the generic and objective SF-36. The WHO has established an international, cross-cultural and cross-population definition of QoL. In an attempt to generify the measure of QoL, the WHOQOL-100 was first created and summarized into the WHOQOL-Bref which contains 26 questions. There is a high correlation (0.89 or more) between the domain scores produced from both these surveys. (45,59) The WHOQOL-Bref was developed to help health

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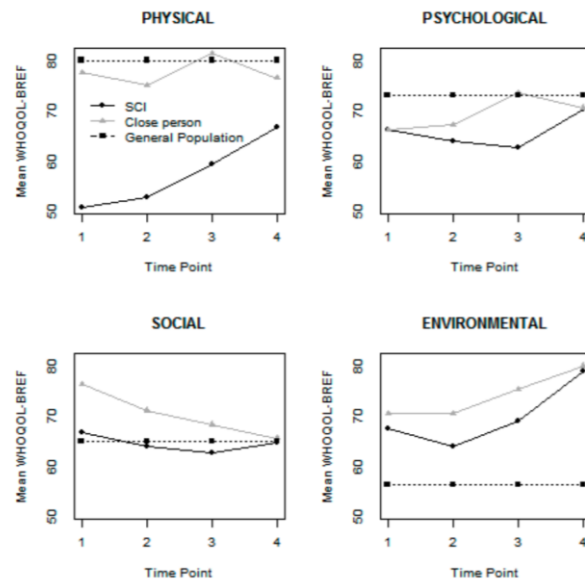Faculté de biologie
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professionals in evaluating the efficacy of treatments in clinical trials. It analyses QoL divided into 4 domains which are as follows and detailed in Table 5: physical health, psychological health, social relationships and environment. In each of these domains and overall, a higher score equals a higher QoL. Scores are initially on a 1 to 5 scale and transformed to a 1 to 100 scale. The WHOQOL-Bref has been validated for use in clinical trials including SCI individuals. The domain scores have a good discriminant and content validity as well as good internal consistency and test-retest reliability.(59,60)

In Lude et al 2014's longitudinal multicentered study of QoL throughout SCI rehabilitation, the WHOQOL-Bref was used and assessed. Lesion level and lesion type had a clear influence on results especially in the physical domain. Another element that affected the physical domain but also had an influence on psychological, social relationships and environment was time (be it 6 weeks to 2 years post injury). As seen in figure 8., all domain scores increase with time. The lesser effect of physical impairment on QoL influenced by adjustment with time to the disability in shown. At the 4th time point in Figure 8, all SCI individual's WHOQOL-Bref scores tend to reach general population scores.

Table 5. WHOQOL-Bref domains. Source: (WHOQOL-Bref scoring instructions)

Domain	Facets incorporated within domains
1. Physical health	Activities of daily living Dependence on medicinal substances and medical aids Energy and fatigue Mobility Pain and discomfort Sleep and rest Work Capacity
2. Psychological	Bodily image and appearance Negative feelings Positive feelings Self-esteem Spirituality / Religion / Personal beliefs Thinking, learning, memory and concentration
3. Social relationships	Personal relationships Social support Sexual activity
4. Environment	Financial resources Freedom, physical safety and security Health and social care: accessibility and quality Home environment Opportunities for acquiring new information and skills Participation in and opportunities for recreation / leisure activities Physical environment (pollution / noise / traffic / climate) Transport

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Figure 8. Mean WHOQOL-Bref scores for each domain at 6 weeks, 12 weeks, 1 year and 2 years post injury the participants (Lude et al. 2014) with spinal cord injury for (SCI) and the close persons, with the mean values in the general population as a reference. Source:(50)

Already included in the study, in order to access functional independence was the SCIM III (Spinal Cord Independence Measure III). The SCIM III consists of 19 items divided into 3 subscales which include self-care, respiration and sphincter management and mobility. The maximum score is 100 meaning the closer the individual is to 100 points, the less assistance in basic activities of daily living he will need.(61) This disability scale was designed particularly for SCI patients and has been repeatedly validated and considered reliable in multi-cultural, multi-centered studies.(62–64) Through this evaluation, the individual´s function and performance in daily activities is weighed. To date, SCIM III is the most sensitive functional independence questionnaire in literature in regards to change. Many functional independence surveys exist. For instance,

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FIM (Functional Independence Measure) is a widely-known and validated questionnaire, but the SCIM III, a SCI-tailored survey, reaches higher sensitivity making it more valuable for the STIMO study.(62,64,65)

After studying the close relationship between SHCs and QoL. We chose to add specific questionnaires assessing sleep (Sleep Quality Assessment PSQI), spasticity (The Spinal Cord Injury Spasticity Evaluation Tool - SCI-SET), bladder and bowel control problems (clinical evaluation in bladder function and the Neurogenic Bowel Dysfunction Score), and sexuality (International Index of Erectile Dysfunction). We use already included questionnaires SPA (Short Pain Assessment) for pain and SCIM III (Spinal Cord Independence Measure III) for functional independence. This questionnaires set is assessed at three time points: before the start of the study, post-rehabilitation and 3 months into the STIMO extension study. One exception is the questionnaire on sex life which is evaluated yearly. The EQ-5D-5L and the Reintegration to Normal Living Index (RNLI) were later added for more specificity in general QoL evaluation, an assessment of the evolution of social participation and because these questionnaires are required in order to obtain reimbursement of new therapies being the standard benchmark for QoL in health economics. During the STIMO extension study, all questionnaires are assessed as a digital survey.

Limitation of some QOL questionnaires are questions that are not adapted to SCI patients (questionnaires about walking distances more than 1km, or running). We did our best to avoid such questionnaires.

What will be interesting in this QoL analysis will be comparing objectified values of functioning (ex. SCIM III) with QoL evolution (both objective and subjective).
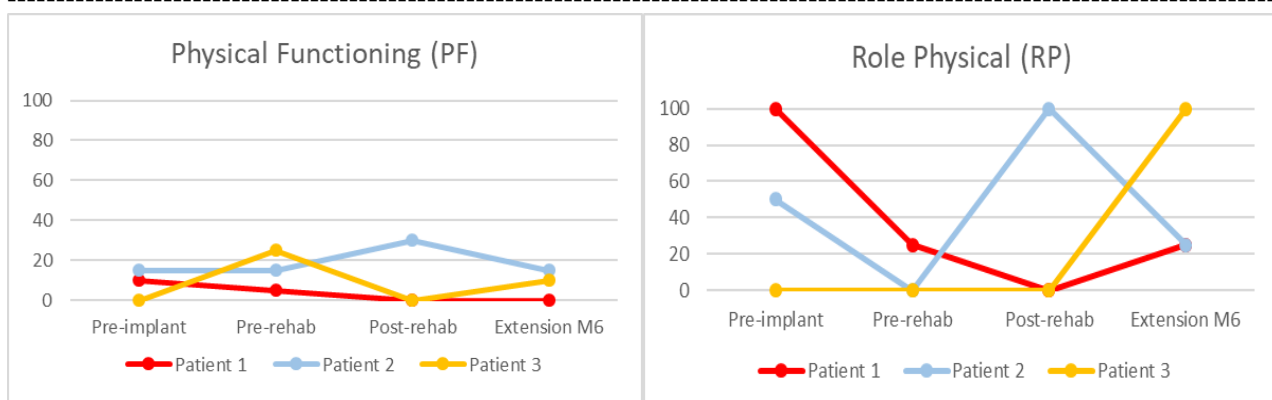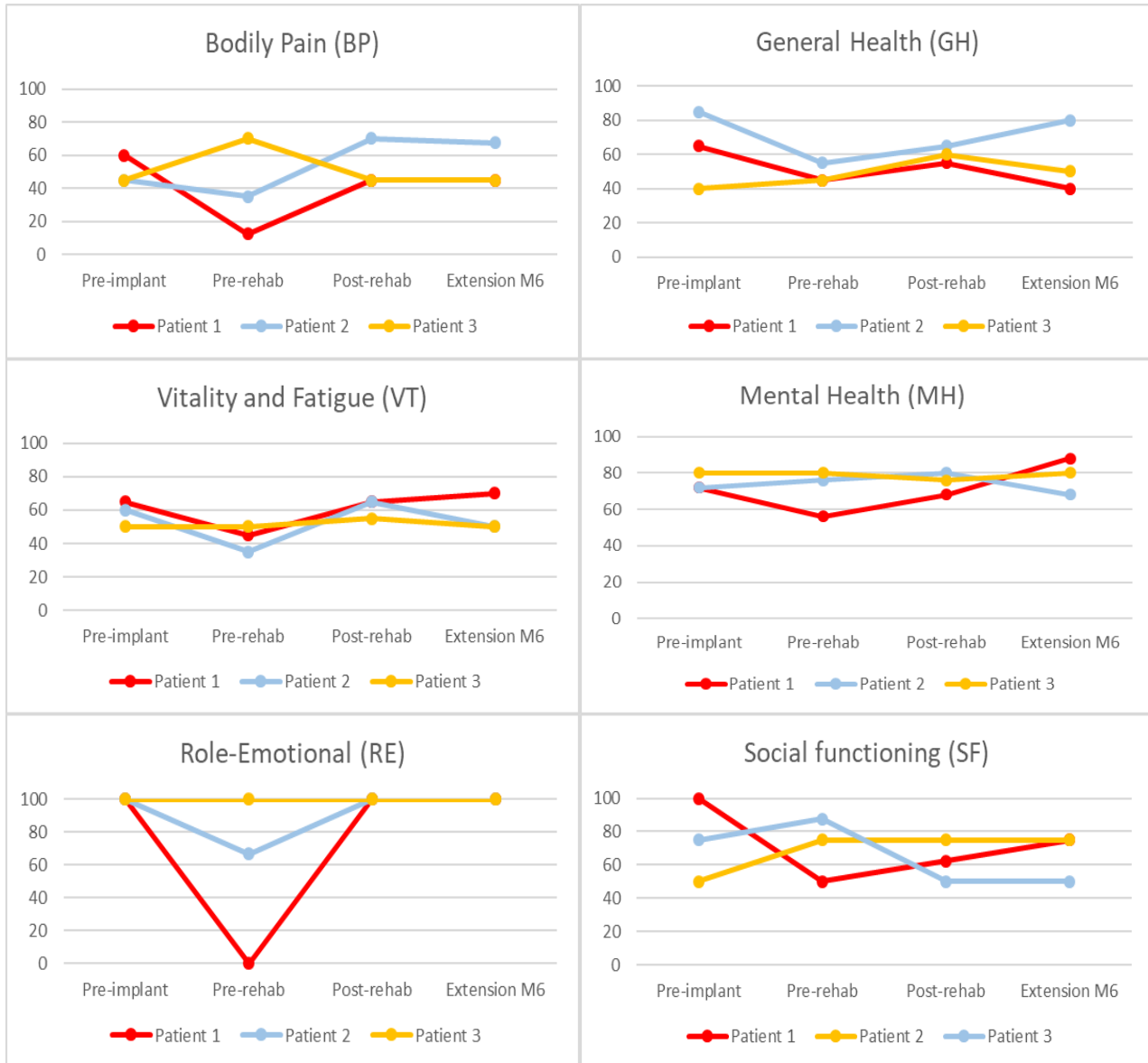
Results

The low number of data points collected at this stage of the study execution and the low number of subjects included in the study will only allow comments on possible trends.

HRQoL Measurements

In STIMO, the SF-36 questionnaire was used at the following four timepoints: pre-implantations, pre-rehabilitation, post-rehabilitation and extension at 6-months (M6) to evaluate HRQoL of our patients. The results are shown in figure 7.

Figure 7. Transformed scores for the 8 domains of the SF-36 survey for patients 1,2,3 at four timepoints throughout the STIMO study: pre-implant, pre-rehab, post-rehab and extension (M6).

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Bodily Pain (BP) — Patient 1, Patient 2, Patient 3

General Health (GH) — Patient 1, Patient 2, Patient 3

Vitality and Fatigue (VT) — Patient 1, Patient 2, Patient 3

Mental Health (MH) — Patient 1, Patient 2, Patient 3

Role-Emotional (RE) — Patient 1, Patient 2, Patient 3

Social functioning (SF) — Patient 1, Patient 2, Patient 3

Physical Functioning (PF)

Throughout the study, in the physical functioning (PF) domain of the SF-36, none of the patients surpass the 40% score or show much variation in this domain. Three different behaviors are observed. Patient 1 shows a gradual decrease to an unanticipated final score of 0%. Patient 2's score is stable at 15% with a transitional doubling in score at post-rehab. Unlike patient 1 and patient 2, patient 3's score at the extension is higher than at the beginning of the study with a slight increase of 10%.

Role limitations due to physical health (RP)

In this domain, all three patients reach the high score of 100% at different timepoints in the study. Patient 1 starts out at 100% but his score decreases as the study moves forwards to a final score of 25% in the extension. Patient 2's high score is reached at post-rehab. Patient 3's score evolution shows a drastic change from post-rehab to the extension time point from 0% to 100%.

Bodily Pain (BP)

The scores in BP vary from the pre-implant to the post-rehab stage but reach a plateau for all three patients from post-rehab to the extension. Patient 1 and patient 2 both initially show a decrease in score at pre-rehabilitation before increasing their score to reach this plateau. Inversely, Patient 3's score increases at pre-rehabilitation but is the same at pre-implant and post-rehab on.

General health

In this domain, both patient's 1 and 2 follow a similar course: an initial decrease from pre-implant to pre-rehab followed by a slight increase from pre-rehab to post-rehabilitation. Both these patients' extension scores are lower than initial pre-implantation score (from 65% to 40% for patient 1 and from 85% to 80% for patient 2). Dissimilarly, patient 3's general health score shows a progressive increase from pre-implant to post-rehab and ends higher at the extension stage than at the pre-implantation stage with a final score of 50%.

Mental Health (MH)

It is important to note that the scores in the MH domain are higher than the 50% mark for all patients throughout the study. Patient 1 reached the lowest score at the pre-rehab timepoint with a score of 56%.

Role limitation due to emotional problems (RE)

In this domain, patient 3 has a constant score of 100%. Both patients 1 and 2 show a decrease at the pre-rehab timepoint (at 0% for patient 1 and at 67% for patient 2), but score at 100% for all other timepoints.

Social Functioning (SF)

The SF domain shows an increase of score for patient 2 from pre-implant to pre-rehab that stays stable forward on. Both patients 1 and 3's scores, however, decrease from pre-implant to the extension stage. The social functioning score for all three patients stay over the 50% mark.

Vitality and Fatigue (VT)

This domain is extremely stable for all three patients. Patient 1 has the highest constant score. Patient 2's score vacillates around the 50% mark. Patient 3's score is extremely constant at 50% to 55% throughout the study.

Table 3. SF-36 MCS at pre-implantation and at the extension stage for three STIMO patients. Scores in %. Computed using method, means and coefficients from :(57,66)

MCS	Patient 1	Patient 2	Patient 3
Pre-implant	61,54	56,78	64,51
Extension M6	68,00	57,60	56,74

Table 4. SF-36 PCS at pre-implantation and at the extension stage for three STIMO patients. Scores in %. Computed using method, means and coefficients from :(57,66)

PCS	Patient 1	Patient 2	Patient 3
Pre-implant	34,45	30,67	15,87
Extension M6	17,79	30,73	29,56

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Physical vs. mental component scores

As previously stated, the 8 domains of the SF-36 can be divided into two categories: PCS vs. MCS. The MCS is shown in table 3. In comparison to the PCS in table 4, the MCS averages much higher and above 50% for all three patients. Although patient 3 shows a decrease in the MCS from the pre-implant to the extension, the variation is not drastic. In the PCS, patient 3 is the only patient whose score increases (12%). This could be in part due to the radical rise from 0 to 100% in RP for this patient; the RP having a positive coefficient in the PCS.

Overall trends

In the STIMO study, patient 1's evolution in HRQoL improves in most domains of the SF-36 questionnaire except domains with a physical component (physical functioning PF and role-physical RP). His evolution shows particular variation in the Role Limitations due to Emotional Problems (RE) domain where a 100% downfall is seen from pre-implant to pre-rehab followed by a symmetrical increase of 100% from pre-rehab to post-rehab and a maintenance of this score in the extension.

Patient 2's strong domain is the BP domain in which a net improvement from 45% at pre-implant to 67,5% is seen. His social functioning score is also the only one that doesn't improve in the post-rehab and extension stages with a loss of points from 80% to 50%.

Patient 3 shows the least variation throughout the study. His scores stay constant with a maximal variation of 25% from one timepoint to another in all domains. The only exception is the role physical domain where a clear improvement from 0% to 100% is seen in the extension stage.

A similar trend is seen for almost all domains and patients: a decrease from pre-implant to pre-rehab followed by a gradual increase in score towards the extension. We could assume that further with more extension timepoints, the scores could exceed the pre-rehab scores for all patients, in continuum of the gradual increase with time post-rehabilitation. The intensive rehabilitation seems to have an important effect on all patient's physical health, bringing scores down. The RE score initial decrease for patient 1 and 2 mirrors the emotional difficulty of adapting to a new environment and living through such an intensive rehabilitation. Although the study is very demanding on a physical basis, the consistency in MCS and even increase in score for patient 1 mirrors the positive effect the study has on a mental health basis for patients who develop new hope of improving their locomotor function.

Subjective QoL Measurements

In STIMO, we used the WHOQOL-Bref for evaluation of our patients' subjective QoL at multiple time points throughout the study: Pre-rehabilitation, Intermediate, Post-Rehabilitation, Extension 1 (corresponding to extension at 3 months post-rehab M3) and Extension 2 (corresponding to the extension at 6 months post-rehab M6). The results are illustrated in Figure 9 below, one graph corresponding to each domain.

Physical domain score

In the physical domain, a decrease is seen for patients 1 and 2 from pre-rehab to the intermediate time point, be it an approximately 30% decrease in physical score for patient 1 and an approximately 20% decrease for patient 2. Patient 3's score does not decrease until the post-rehab timepoint (5% decrease). Patient 3 has the highest final score and is the only patient to score higher at the extension stage than at the entry into the trial at pre-rehab with a score going from 71% pre- rehab to 79%, meaning a 8% overall increase of score. Patient 1's scores decrease of approximately 5% from pre-rehab to the second extension, be it from 71% to 64%. Patient 2's score goes from 67% to 63%, be it a variation of 4%.
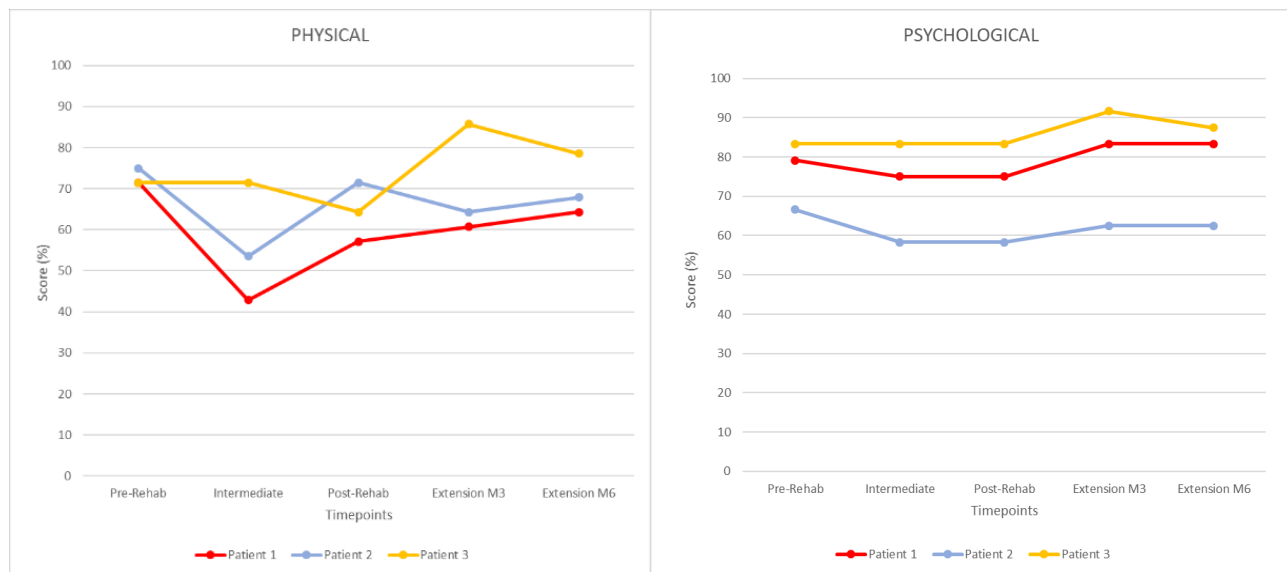
Psychological domain score

The psychological domain in STIMO shows less variation than the other domains for all three patients. The results nearly stay constant throughout the study with less than a 5% difference from one timepoint to another

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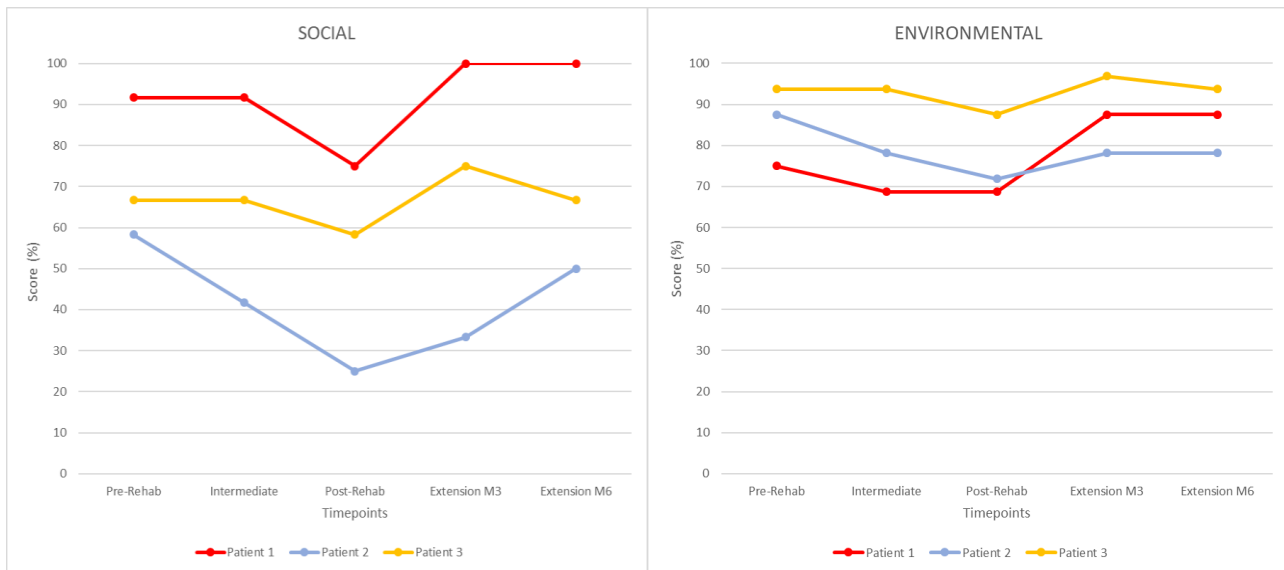Faculté de biologie
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for each patient. Except for patient 2's score that decreases from 67% at pre-rehab to 63% at post rehab, final scores at the second extension timepoint are slightly higher than initial scores at pre-rehab which shows a slightly favorable psychological evolution following the rehabilitation. Patient 1's transformed psychological score at the 6-month extension is 83% whereas his initial score at pre-rehabilitation was 79%. Patient 3's initial score is 83% and slightly improves to a score of 88% at the second extension timepoint.

Social domain score
All three patients scores decrease at post-rehab to improve in the extension. This domain shows an important inter-individual difference in scores. Patient 1's scores throughout the study stay over the 75% mark whereas patient 3's scores range from 58% (post-rehab) to a maximum of 75% (extension 1). Patient 2 has the overall lowest scores with a range from 25% to 58% and has a lower score at the 6 months extension than at the pre-rehab timepoint. Both patients 1 and 3 show an improvement or stabilization in the social domain score from pre-rehab to the second extension (92% to 100% for patient 1 and stabilization at 67% for patient 3). This domain is the only one in which the highest possible score of 100% is reached for patient 1 at the second extension.

Figure 9. Transformed WHOQOL-Bref scores for each domain at pre-rehab, intermediate, post rehab, extension 1 and extension 2 for patients 1, 2 and 3 of the STIMO study.

SOCIAL / ENVIRONMENTAL — Score (%) by Timepoints (Pre-Rehab, Intermediate, Post-Rehab, Extension M3, Extension M6) for Patient 1, Patient 2, Patient 3.

Environment domain score

Similar to the psychological domain, the environmental domain is one of the domains seemingly lesser influenced by the STIMO rehabilitation. From one timepoint to another, the maximal variation is for patient 1 from post rehab to the first extension timepoint with an increase of 19%. Patient 3's score is the most constant with a maximal 6% decrease at post-rehab followed by a max 9% increase at extension. The minimal score is at post-rehab after which an increase in score is seen for all three patients.

Overall trends

The following trends can be observed for all domains of the WHOQOL-Bref questionnaire in STIMO. Scores for all patients drop in response to the intensive rehabilitation. The rehabilitation is extremely demanding. The patients are far from family and friends and have to adapt to a new environment in Lausanne where they live for the time of the rehabilitation. This affects the social and environmental scores.

Patient 1 has a tendency of scoring higher after the STIMO intervention than at the beginning of the trial in all domains except the physical domain. Patient 3's scores are the same at pre-rehab and at the extension stage except for an increase in the physical domain score. Patient 2's scores in each domain are lower at the extension stage than the beginning of study. His overall WHOQOL-Bref score stays constant (at 75%). Inversely, patient 3 and patient 1's overall scores are lower at the extension stage than at pre-rehab with a 25% decrease. [table 6]. Most of the improvement for all three patients is seen at the extension stage showing the importance of such stage and a good follow up. We could expect to have a continuation of this gradual increase in WHOQOL-Bref scores in all domains at further timepoints in the extension. The little variations in score for the social and environmental domains shows the difficulty of quantifying subjective QoL. The initial scores for all patients in all domains having all reached higher than the 50%, a ceiling effect must be expected. A variation in subjective QoL is harder to bring forth for STIMO chronic SCI patients.

Table 6. WHOQOL-Bref Overall transformed scores for STIMO patients 1,2 and 3 at pre-rehabilitation, intermediate, post-rehabilitation, first extension (M3) and second extension (M6).

ID	Timepoint	Overall Score		ID	Timepoint	Overall Score		ID	Timepoint	Overall Score	
		Raw	Transformed			Raw	Transformed			Raw	Transformed
1	Pre-Rehab	8	75,0	2	Pre-Rehab	8	75,0	3	Pre-Rehab	8	75,0
1	Intermediate	7	62,5	2	Intermediate	6	50,0	3	Intermediate	8	75,0
1	Post-Rehab	8	75,0	2	Post-Rehab	6	50,0	3	Post-Rehab	7	62,5
1	Extension M3	8	75,0	2	Extension M3	8	75,0	3	Extension M3	8	75,0
1	Extension M6	6	50,0	2	Extension M6	8	75,0	3	Extension M6	6	50,0

Functional independence

Functional independence in the STIMO study is evaluated with the Spinal Cord Independence Measure III (SCIM III) at the following timepoints: pre-rehab, intermediate, post-rehab and two extensions (M3 and M6). The results of evolution of functional independence are illustrated in Figure 10 below. Unfortunately, the second extension data is not available at this time for patient 3.

Figure 10. SCIM III scores for each subscale at 5 different timepoints throughout the STIMO study: pre-rehab, intermediate, post-rehab, first extension (M3) and second extension (M6).

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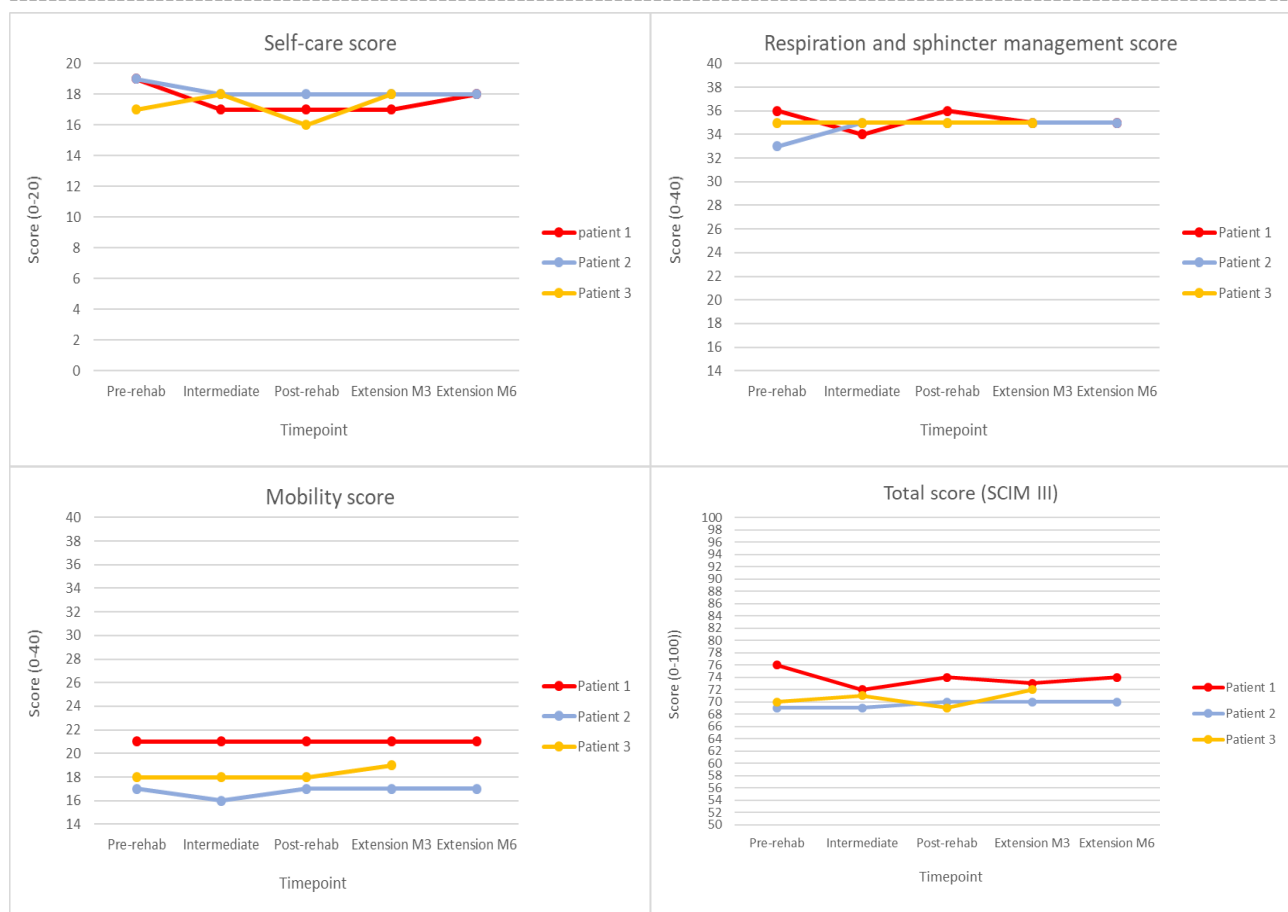
Self-Care

In the Self-Care sub-scale of SCIM III, both patients 1 and 2 loose points from pre-rehab to the intermediate stage and do not regain these points further along. Patient 1's score decreases by 2 points from 19/20 to 17/20 whereas patient 2's score diminishes by only 1 point. Patient 2's scores are more variable. He is the only patient whose final score at the second extension is higher at 18/20 than his initial score at pre-rehab at 17/20. Note the score for this domain is on 20 points maximum and all three patients score higher than 16/20 at each time point, over the 50% mark.

Respiration and sphincter management

In this sub-scale of the SCIM III, patient 3's score shows no evolution from one timepoint to another. Patient 1's final score at the second extension is one point lower than initially at pre-rehab and patient 2's score rises by 2/40. All patients are over the 33/40 points placing them in the highest ¼ of respiration and sphincter management domain. All three patients end up with the same score at 35/40 from the first extension point on.

Mobility

In mobility, very little evolution is shown for all three patients. Patient 1's score stays constant at 21/40 points throughout the trial. Patient 2's score is almost constant at 17/40 except for a decrease at 16/40 at the intermediate timepoint. Patient 3's constant score increases by one point from 18 to 19/40 at the first extension. Scores in mobility are very low for all patients unlike both the self-care sub-scale score and the respiration and sphincter management sub-scale score. All scores are less than 22/40 and patient 2 and 3's scores are less than 50% throughout the study with the highest reached score for patient 2 being at 17/40 and the highest score for patient 3 being at 19/40.

Overall Trends

The total SCIM III score in STIMO shows minimal changes. The lowest reached total score is 69% for patient 2 at the intermediate time point and for patient 3 at post-rehab. All three patients are over the 50% bar in total SCIM III score showing a rather high initial functional independence score. Because this score is already very high in comparison to the general population, ceiling effect must be taken into consideration. As previously mentioned, having a significant change in score is difficult for chronic SCI patients. Evolution in all 3 sub-scales is limited throughout the study with a maximal variation of 2-3 points from one time point to another. No drastic variations are observed in functional independence.

STIMO patients vs. RHI general database

The Rick Hansen Institute based in Vancouver, Canada is a non-profit organization specialized in SCI research and management. They work to collect data on SCI patients and have created an important database. This allows the comparison of results obtained in the STIMO study with results from patients following a standard rehabilitation. (68) As seen in figure 11 and 12 below, the comparison of SCIM III results was possible by selecting data in relation to individuals with ASIA C, lesion C5-C8, the same category in which STIMO patients fall. The RHI data for SCIM III used here includes two different timepoints: pre-rehab and community follow up. Wanting to compare evolution of STIMO patients to evolution of RHI patients from pre-rehab to the extension phase which could be paralleled with RHI community follow up, the three STIMO patients' scores at pre-rehab are compared to RHI data range. As expected, STIMO patients at pre-rehab fall in the data range for RHI community follow up rather than in the RHI pre-rehab data range. We know STIMO patients are chronic, because they are all at 4 to 7 years post SCI. This comparison confirms this chronic stage and that STIMO individuals have already adapted to SCI: response shift has occurred. This means QoL in STIMO patients are more similar to the general population's QoL scores than to QoL scores of acute SCI patients. (>50% scores) Because these chronic individuals have already reached higher HRQoL scores through response shift, the new baseline met is difficult to change: ceiling effect. Indeed, in acute patients, these two phenomena

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would be avoided. Acute SCI individuals could show more significant evolution in QoL. When comparing STIMO scores of SF-36 at pre-implant with RHI community follow up scores and SF-36 at the 6-month extension with RHI community follow up [see figure 13 and 14], STIMO individual's evolution or rather non-evolution in MCS and PCS scores is seen. STIMO individuals mostly stay in RHI data range from one time point to another and don't show much evolution. Further time points and further patients may show progression in comparison to community follow up of SCI patients from RHI database.

Figure 11. STIMO Patients SCIM III score at pre-rehab timepoint in comparison to RHI data range with assumption of symmetry at the pre-rehab timepoint (selection of ASIA C, lesion C5-C8 patients included in data)

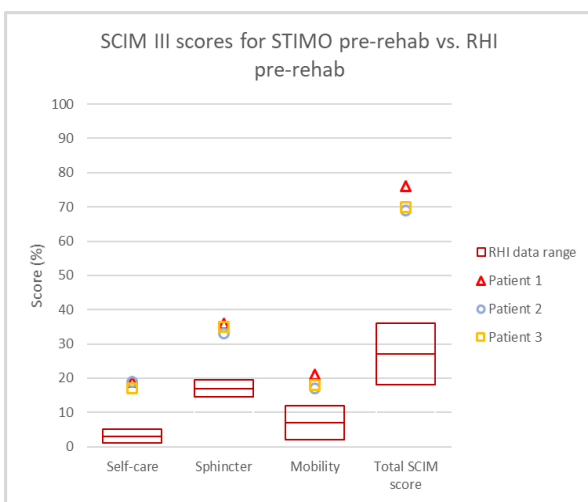---

Figure 12. STIMO Patients SCIM III score at pre-rehab point in comparison to RHI data range with assumption of symmetry at community follow up (selection of ASIA C, lesion C5-C8 patients included in data).

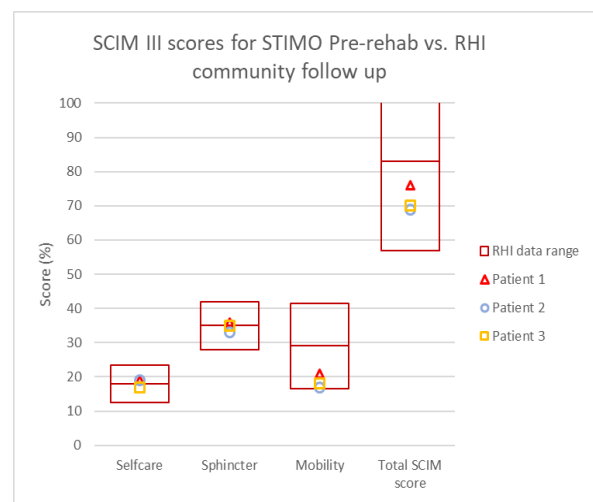---

Figure 13. STIMO patients SF-36 total score at pre-implantation in comparison to RHI data range with assumption of symmetry at community follow-up (selection of ASIA C, lesion C5-C8)
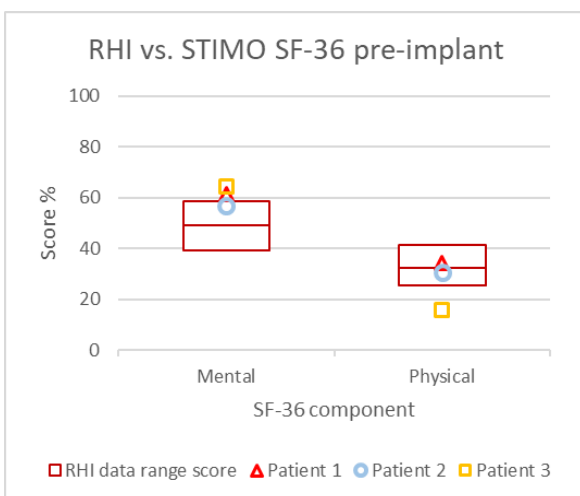

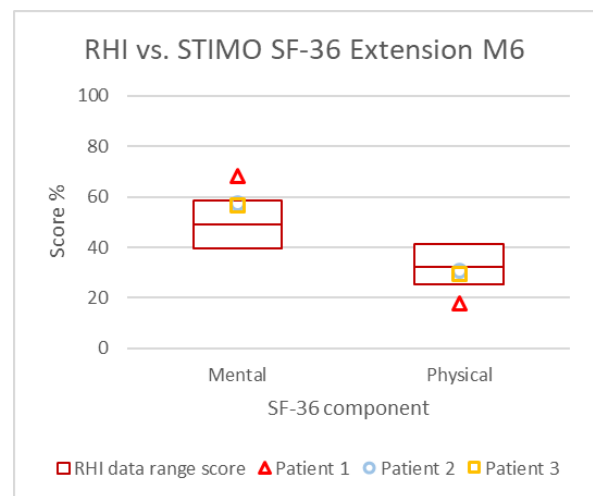---

Figure 14. STIMO patients SF-36 total score at pre-implantation in comparison to RHI data range with assumption of symmetry at community follow-up (selection of ASIA C, lesion C5-C8)

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Discussion

Physical Scores in Objective, Subjective QoL, and Functional Independence

SCIM III Total vs. SF-36 PF

In comparing the PF domain in the SF-36 [figure 7] to the Total Score for the SCIM III [figure 10], an important difference is seen between the two scores that are both evaluated in %. The PF domain of the SF-36's scores are very low, under 35% for all three patients, even reaching 0% for patient 1 and 3 at post-rehab and patient 1 at the second extension (M6). The PCS of objective QoL for all patient's is very low [see table 4]. Total SCIM III score shows values higher than 65% for all patients at all timepoints. The evolution from one timepoint to another [as seen in figure 15 below], is at maximum 25% of variation for PF of the SF-36 and less than 10% of variation in the Total SCIM III score. In comparing HRQoL with functional independence, although all patients' trajectories tend to be similar, (an increase from pre-rehab to post-rehab for patient 2 followed by a decrease from post-rehab to the extension at 6 months; a decrease for patient 1 from pre-rehab to post-rehab followed by an increase from post-rehab to the extension at 6 months), HRQoL is more sensitive to change in the STIMO study.

SCIM III Total vs. WHOQOL-Bref Physical

The SCIM III total score, objective and clinical trial observer tested, is in concordance with the physical domain of WHOQOL-Bref. Maximal variation from one timepoint to another is 25% in the WHOQOL-Bref compared to a small variation of 4% in the total SCIM III scores [figure 16]. The trajectories in both scores are similar but rehabilitation in STIMO has a more important effect on subjective well-being than functional independence. As expected with subjective QoL evaluation, the WHOQOL-Bref is more sensitive to change than functional independence. Domain importance included in subjective well-being shows its effect here. The effect of intensive rehabilitation is observed with the decrease in scores for all patients in subjective well-being (at intermediate for patient 1 and patient 2 and at post-rehab for patient 3).

Figure 15. SCIM III Total scores vs. SF-36 PF scores for patients 1, 2 and 3 of STIMO at pre-rehab, post-rehab and at extension (M6).

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Figure 16. SCIM III total scores vs. WHOQOL-Bref physical domain scores for patients 1, 2 and 3 of STIMO at pre-rehab, intermediate, post-rehab and at extension (M6).
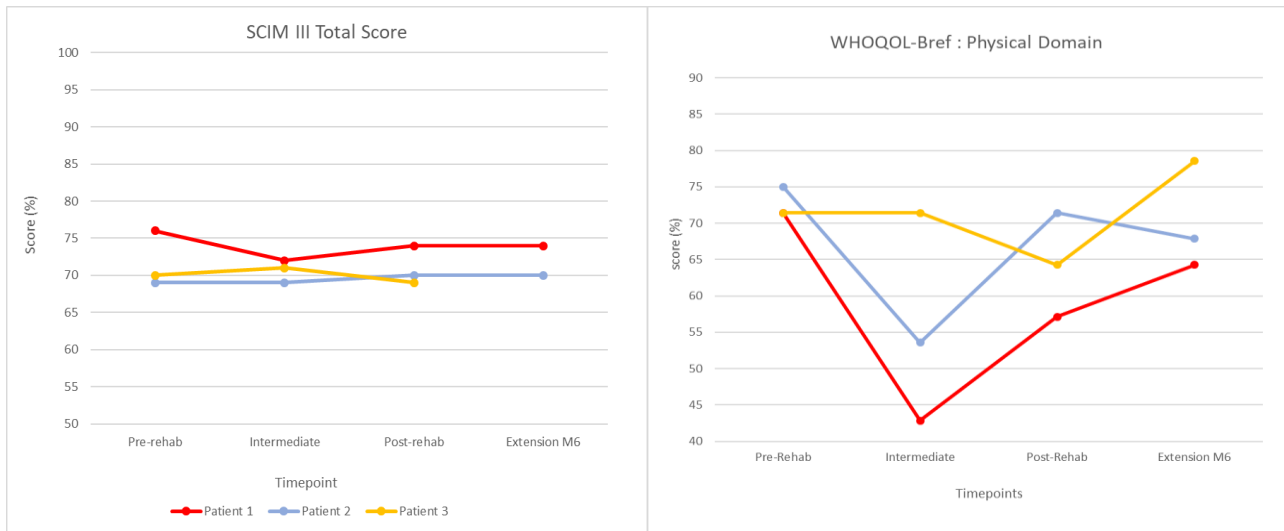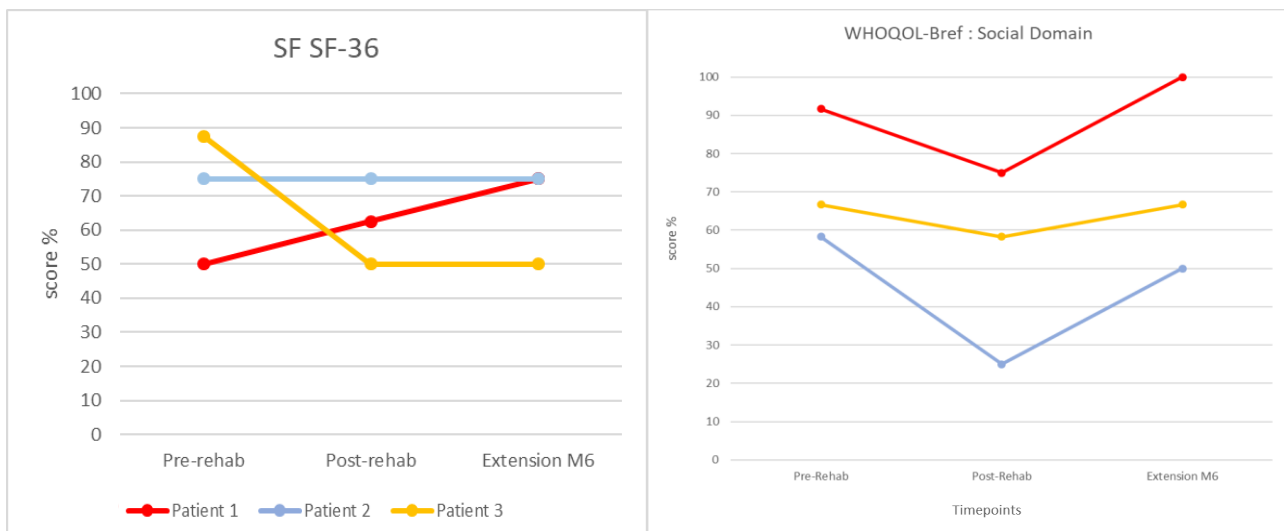

Figure 17. SF-36 Social Functioning (SF) scores vs. WHOQOL-Bref social domain scores for patients 1, 2 and 3 of STIMO at pre-rehab, post-rehab and at extension (M6).


Social and Psychological scores in objective vs. subjective QoL evaluation

WHOQOL-Bref social domain vs. SF-36 SF and psychological domain vs. SF-36 MH

Depending on the patient, evolutions in SF and MH scores of the SF-36 follow variable trajectories. For HRQoL, it is difficult to appreciate a common trend between patients for these domains [see Figure 17 and 18]. Similar trajectories are recurrent in WHOQOL-Bref social and psychological domains. Through subjective QoL and domain importance, the psychological and social toll from the rehabilitation can be identifies by a fall of both scores at post-rehab for all patients although the impact is more or less severe

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depending on the patient. All 3 patients' commitment is remarkable. They moved away from their homes, work, family and friends in order to participate in the study as they do not come from or live in Lausanne or in close proximity to the training site at the CHUV. The rehabilitation program includes walking on a treadmill and over-ground as well as strengthening muscles and standing, enabled by task-specific EES. This intensive rehabilitation is repeated four to five days weekly.(55)

Figure 18. SF-36 Social Functioning (SF) scores vs. WHOQOL-Bref physical domain scores for patients 1, 2 and 3 of STIMO at pre-rehab, post-rehab and at extension (M6).
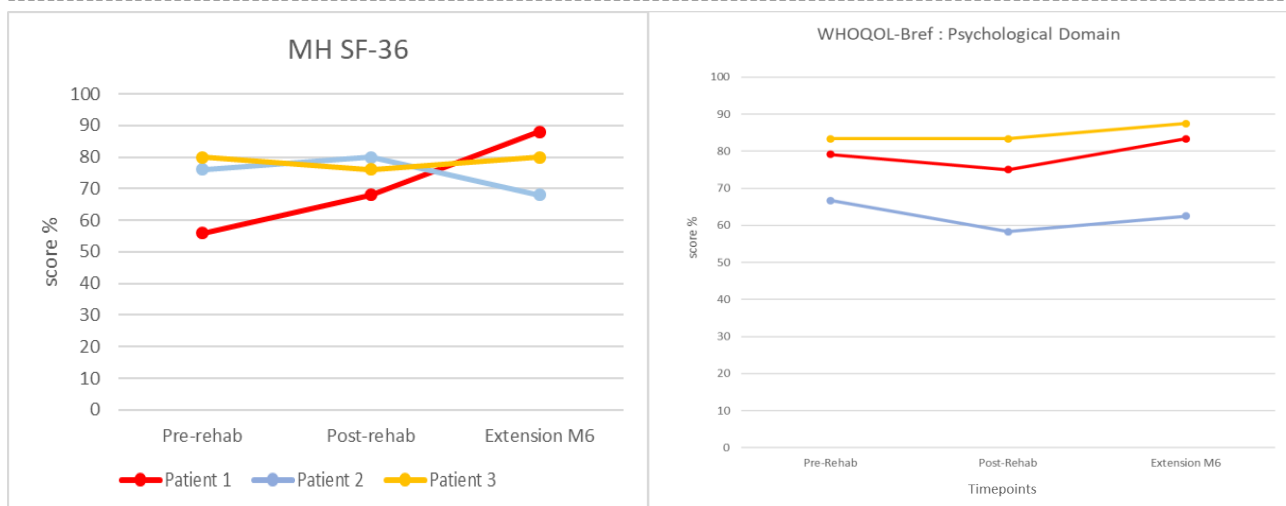

Motor function vs. functional independence and subjective QoL

In STIMO, locomotor function improved during rehabilitation. Without EES, progressively throughout and following the rehabilitation, voluntary control over paralyzed muscles was regained. The WISCI (walking index for spinal cord injury) and clinical evaluation by walking speed (ten-meter walking test) and endurance (six-minute walking test) were included to study motor function. (55) As seen in Wagner et al. 2018, post-rehabilitation without EES, patient scores for the WISCI increase from 13 to 15 for patient 1 and from 6 to 13 for patient 2. Clinically, both patient 1 and 2 could move from sit to stand and walk with crutches. As seen in figure 19.a., the ten-meter and six-minute walking test improve greatly for all patients throughout the rehabilitation and continue to improve post-rehabilitation (both participants continue to use EES in rehabilitation 1-2 times a week).(55) In comparison with SCIM III [figure 19.c] results, the significative advancement seen with the increase in neuromotor function is difficult to translate into functional independence. Variation in functional independence is extremely limited. The 6-month extension score does not surpass the pre-rehab score even for patient 1 who could walk a few steps without any assistive devices at the post-rehabilitation stage.(55) In comparing with the WHOQOL-Bref Physical scores [figure 19.b.], from pre-rehab to the intermediate stage, the positive evolution of endurance and walking speed is opposite to the initial negative evolution seen in subjective QoL. Final scores of subjective QoL at the 6-month extension generally do not or barely surpass scores before the rehabilitation. If the study has no significant impact on subjective QoL, the clinical relevance of this significant motor function improvement is put into play. Parallelly, the relevance of studying QoL in chronic SCI patients who already have a subjective QoL resembling the general population's therefore limited space for improvement is posed.

Because the rehabilitation stage takes such a toll on subjective QoL for all three patients and the recovery following the intervention follows a slow progressive upward slope, it's difficult to evaluate at this point, without a longer-term follow-up the final effects of the trial. In the extension, patients tend to higher QoL. The

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progression is still non-significant at this stage. With more data points as well as more patients, a clearer slope will probably be evaluable.

Figure 19. a. Plot reporting changes in 6-min and 10-m walk tests for P1 (patient 1) and P2 (patient 2). Tests were performed without gravity-assist, following clinical guidance. For P3 (patient 3) plots report changes in walking distance during rehabilitation and waking speed in EES (with transparent body weight support.) Source:(55). b. WHOQOL-Bref scores score for patient 1,2 and 3 at pre-rehab, intermediate, post-rehab. Extension at 3 months, extension at 6 months. c. Total SCIM III scores for patients 1,2 and 3 at pre-rehab, intermediate, post-rehab. Extension at 3 months, extension at 6 months.
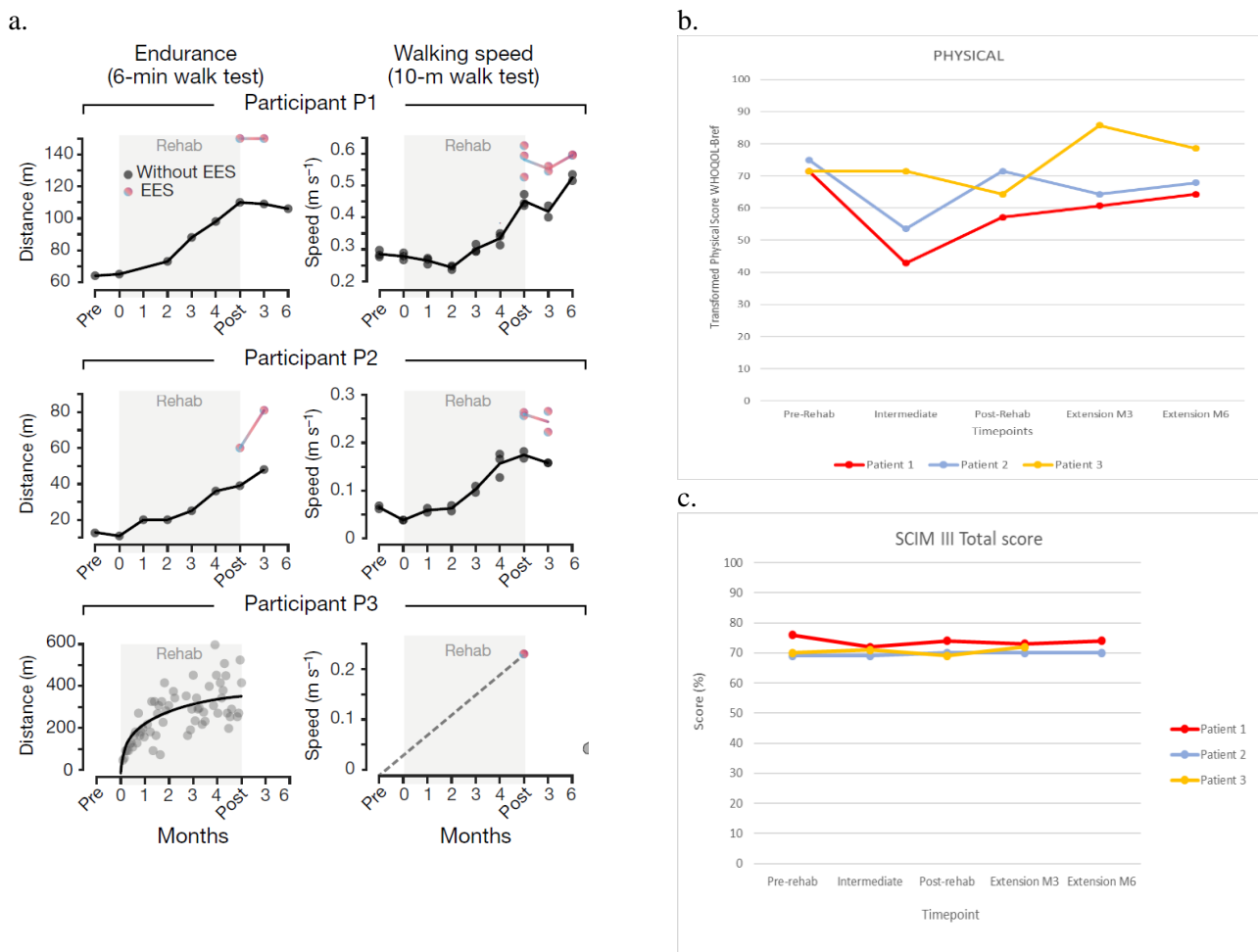
Conclusion

As expected, subjective QoL is the most responsive to change in the STIMO study. This is proof that a clear definition of the type of QoL being evaluated is important in SCI and in all studies. Many times, subjective well-being is forgotten in analysis of SCI QoL even though it's score can differ from objective QoL.

In the STIMO study evolution, one main trend is seen in the evaluation of QoL, be it HRQoL and subjective QoL. Very much every aspect of QoL suffers a decrease in scores at the intermediate or post-rehab stage of the study, mirroring the difficulty of the STIMO study rehabilitation, especially in subjective QoL. After this

score drop during the rehabilitation, all patients tend to higher their QoL scores gradually yet still non-significantly in the extension stage. Additional timepoints and patients could allow a re-evaluation of the evolution of objective and subjective QoL throughout the study. With time, patients would possibly further improve their scores and show a net improvement from pre-rehab to the further extension stages.

Because STIMO patients are chronic SCI patients, being at 4 to 7 years post-injury, the process of adaptation has already occurred. STIMO patients have reached a QoL baseline similar to that of the general population. High scores in subjective QoL and the comparison of SCIM III and SF-36 scores with the RHI database putting STIMO patients at community follow up rather than pre-rehabilitation, makes for a ceiling effect. Net motor function improvements at this stage are difficult to translate into equal enhancement of QoL. The absence of significant positive impact on QoL questionnaires thus far lets us ponder the question of clinical relevance at this stage of SCI. However, is there a utility in considering evolution of QoL as a vital factor for clinical relevance in chronic SCI patients with a baseline QoL already so similar to QoL in the general population?

If the study included acute SCI patients, their subjective QoL would not yet have undergone adaptation. Acute patients tend to have a much lower initial QoL score, there would be no ceiling effect. Because it is expected that acute patients show more enhancements of locomotor function, in parallel, QoL questionnaires should be able to bring to light significant improvements.

Future investigations

As already stated, a higher number of patient inclusion and a longer term follow up will allow for more data analysis and concretization of current trends.

In order to change the evaluation of QoL to fit STIMO needs, the questionnaire set was added for more specific evaluation of SHCs. However, this questionnaire set was not analyzed in this QoL evaluation due to limited data and late inclusion of the questionnaires in the study. The set includes specific questionnaires for pain (SPA), sleep (Sleep Quality Assessment PSQI), spasticity (The Spinal Cord Injury Spasticity Evaluation Tool - SCI-SET), bladder and bowel control problems (clinical evaluation in bladder function and the Neurogenic Bowel Dysfunction Score), and sexuality (International Index of Erectile Dysfunction). A thorough follow-up in the extension stage has been put together with a fill at home e-survey including all these QoL questionnaires. By separating the analysis of each important SHCs that effect QoL in chronic SCI, trends and evolution could be more sensible to variation and show significant improvements.

The effect of certain variables in STIMO on QoL could also be further detailed. For instance, development of muscular tissue and improvement of orthostasis with a better regulated blood pressure with rehabilitation and verticalization can have positive effects on health and SCI morbidity (67) and effects individuals' QoL to a certain measure.

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