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Review

# Development of quantitative and sensitive assessments of physiological and functional outcome during recovery from spinal cord injury: A Clinical Initiative

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ABSTRACT

The ability to detect physiological changes associated with treatments to effect axonal regeneration, or novel rehabilitation strategies, for spinal cord injury will be challenging using the widely employed American Spinal Injuries Association (ASIA) impairment scales (AIS) for sensory and motor function. Despite many revisions to the AIS standard neurological assessment, there remains a perceived need for more sensitive, quantitative and objective outcome measures. The purpose of Stage 1 of the Clinical Initiative was to develop these tools and then, in Stage 2 to test them for reliability against natural recovery and treatments expected to produce functional improvements in those with complete or incomplete spinal cord injury (SCI). Here we review aspects of the progress made by four teams involved in Stage 2. The strategies employed by the individual teams were (1) application of repetitive transcranial magnetic stimulation (rTMS) to the motor cortex in stable (chronic) SCI with intent to induce functional improvement of upper limb function, (2) a tele-rehabilitation approach using functional electrical stimulation to provide hand opening and grip allowing incomplete SCI subjects to deploy an instrumented manipulandum for hand and arm exercises and to play computer games, (3) weight-assisted treadmill walking therapy (WAT) comparing outcomes in acute and chronic groups of incomplete SCI patients receiving robotic assisted treadmill therapy, and (4) longitudinal monitoring of the natural progress of recovery in incomplete SCI subjects using motor tests for the lower extremity to investigate strength and coordination.


**Contents**



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## 1. Introduction

Spinal cord injury (SCI) is a devastating condition that results in dysfunction or complete loss of function in motor, sensory and autonomic systems that is usually enduring [27]. Present day clinical and rehabilitation practice ensures that life expectancy after SCI approaches that of the able-bodied population [47]. This has important socio-economic implications that are becoming a significant drive towards the development of treatments for recovery of function. Functional recovery could be achieved by interventions that re-innervate disconnected systems or promote the natural plasticity of the central nervous system to facilitate the actions of surviving neurons that have retained axonal connections with their targets [8]. Several of these approaches are currently being translated from bench to bedside.

However, the outcome measures available to monitor any change resulting from an intervention are limited in the required sensitivity to pick up changes over time [17]. The International Spinal Research Trust launched their Clinical Initiative in 2000, the aim of which was to develop procedures for the assessment of functional recovery following SCI. Since it was recognised that experimentally induced regeneration of spinal cord axons in animals had achieved regrowth over a few centimetre at most [44,45,54] protocols for assessing the outcome of such treatments in man might need to detect regeneration over one or two segments [58]. This would be challenging using the widely employed International Standards for Neurological and Functional Classification of Spinal Cord Injury according to the American Spinal Injuries Association (ASIA). Minimally detectable change in the psychometric properties of the ASIA standards in assessing motor and sensory function was not reported in any of the procedures reviewed recently [29]. Despite many revisions to the ASIA standards [3,4], and refinements such as separate upper and lower extremity motor scores [31,46], there remains a perceived need for quantitative and objective outcome measures to supplement the ASIA standards of clinical assessment [56]. There is also a desire for these measures to provide mechanistic evaluations of changes in the nervous system and in sensorimotor function resulting from treatments.

A second stage of the International Spinal Research Trust Clinical Initiative commenced in 2006 and involved teams in London (UK), Zurich (Switzerland), Edmonton (Canada) and Glasgow (UK). The aim was to examine the psychometric properties of newly developed and improved outcome measures from Stage 1 [26], particularly physiological and functional tests, during either the application of treatments expected to produce functional improvements in SCI or the natural course of recovery. This review draws on the experiences gained by the teams involved in Stage 2 of the Clinical Initiative.

### 1.1. Proof of principle and underlying mechanisms of treatments

The population of people with a SCI is very heterogeneous. Consequently, the design of novel Phase I or II clinical trials incorporating interventive treatments to promote functional recovery from spinal cord injury is likely to vary considerably depending upon the particular target of the agent(s) involved and the type of patient to be treated [41]. Indeed, there may be multiple targets as the issues involved in SCI are several, and it is reasonable to anticipate therapies may differentially act on these. Therefore, besides quantifying the outcome, it would be prudent for Phase I and II trials to develop assessment tools that would also contribute to understanding the mechanisms by which any treatment is acting, as this would strengthen the basis of the experimental medicine approach [55].

### 1.2. Confounding issues

Experience has shown that changes in physiological, clinical and functional outcome measures will not always correlate. In previous longitudinal studies of the natural recovery from SCI [16,55] neurological (ASIA) scores improved progressively and tended to stabilise by around 300 days post-injury. In contrast, measures of corticospinal function, such as the threshold and latency of the motor evoked potential (MEP), although significantly different from control values, remained stable resulting in no correlation between clinical assessment and electrophysiological data over time. Similarly, no significant changes in somatosensory evoked potential latencies have been revealed over fifty weeks of significant clinical and functional recovery in incomplete SCI [16]. However, a lack of correlation between physiological and clinical or functional measures is no reason for abandoning newly developed tools for assessing recovery. Electrophysiological results could indicate the underlying systems or pathways targeted by the intervention and, in doing so, provide useful insight into the mechanism of action. Such data will be important for the refinement