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Viewpoint

Recruitment Challenges in Spinal Cord Stimulation Trial for Motor Recovery in Patients with Chronic Complete Spinal Cord Injury

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Abstract: Recruiting participants for clinical trials targeting specific populations, like patients with chronic motor complete spinal cord injuries (SCIs), is challenging. The RESTORES trial evaluated spinal cord stimulation (SCS) combined with robotic neurorehabilitation for motor recovery in this population. This feasibility study enrolled three participants to assess SCS implant safety, synergistic effects of SCS and robotic rehabilitation, and clinical outcomes. Key recruitment barriers included the small patient pool, stringent eligibility criteria, patient skepticism, and logistical and emotional challenges. Strategies to address these challenges encompassed multidisciplinary collaborations with clinical centers, SCI associations, and patient support groups, including pre-surgical counselling and transparent communication. A dedicated clinical research coordinator ensured ethical compliance, logistical support, and participant engagement. Travel reimbursements, family involvement, and peer advocacy fostered accessibility and trust. Of the 115 patients screened, only 3 met the strict eligibility criteria, due to high screening failure rates and participant apprehension. Peer testimonials and family support helped enhance motivation and adherence. Ethical safeguards, like a data safety monitoring board, ensured participant safety and transparency. The RESTORES trial underscores the complexity of recruiting for pioneering interventions while highlighting the importance of tailored, patient-centric strategies. Insights gained will inform future trials and contribute to advancing SCI rehabilitation, offering hope for enhanced neurological recovery and quality of life for individuals with chronic motor complete SCI.

Keywords: spinal cord injury; epidural spinal stimulation; neurosurgery; recruitment challenges; eligibility criteria; patient apprehension; neurorehabilitation; clinical research coordinator; research ethics

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1. Introduction

Recruitment for clinical trials is a critical yet often challenging aspect of trial success, particularly when the target population is highly specific (such as patients with chronic spinal cord injuries (SCIs)), and the burden of participation is substantial for both the patient and their caregivers. In our RESTORES (RESToration Of Rehabilitative function with Epidural spinal Stimulation) trial [1], which focuses on combining spinal cord stimulation (SCS) with advanced robotic neurorehabilitation for motor recovery, recruitment challenges are amplified by the complexity of the condition, patient hesitancy, logistical barriers, and stringent eligibility criteria.

During the RESTORES trial, we hypothesized that combining SCS with advanced robotic neurorehabilitation can improve neurological function in patients with chronic motor complete SCI. The primary aim of this Phase I study was to assess the safety of the SCS implant, considering its off-label usage, in three patients with chronic motor complete SCI. Our secondary aims were to evaluate the synergistic potential of SCS and robotic neurorehabilitation in restoring volitional motor activity and achieving further clinical improvements, such as enhanced autonomic functions and independent locomotion. To meet these objectives, three patients were recruited to undergo customized SCS programming alongside a perioperative locomotor rehabilitation program.

Initially approved by the US FDA for chronic pain management [2,3], SCS has since evolved as a promising intervention for modulating neuronal activity in SCI [4–6]. Despite the therapeutic potential of combining SCS with advanced rehabilitation techniques, patient recruitment remains a significant challenge. SCI patients and their caregivers face considerable physical and emotional burdens, making participation in clinical trials particularly demanding. These difficulties are exacerbated by the need to balance safety and resource management, especially for an intervention like SCS, which involves invasive procedures and long-term follow-up. Moreover, strict eligibility criteria—while essential for ensuring study integrity—often lead to high screening failure rates, reducing the number of eligible participants and extending recruitment timelines [7]. Budgetary constraints and patient apprehension, especially in first-in-man trials, further complicate the recruitment process [7,8].

Understanding and addressing these barriers is essential for ensuring the success of this and similar trials in this patient population, as well as advancing therapeutic developments for SCI. Overcoming these multifaceted associated challenges are key to the trial's success. Ensuring informed consent, patient compliance, and adherence to ethical recruitment practices are critical components that will be further explored in this paper.

2. Methods

2.1. Addressing the Limited Patient Population and Strict Eligibility Criteria

The annual incidence of chronic motor complete SCI is approximately 23 cases per million population [9]. This low incidence rate results in a relatively small pool of potential candidates for clinical trials, particularly those requiring stringent inclusion criteria. For the RESTORES trial [1], the highly specific eligibility requirements—targeting patients with chronic, motor complete SCI—was critical to ensuring patient safety and scientific validity of the trial. However, this also further limited the number of eligible participants. However, these strict criteria further constrained the pool of eligible participants, creating significant recruitment challenges.

To address these barriers, the study team implemented a multifaceted approach to maximize recruitment efforts. Central to this strategy was collaboration with multiple clinical centers specializing in SCI treatment and rehabilitation across Singapore [7]. Leveraging on the country's well-integrated rehabilitation network, clear inclusion and exclusion

criteria (Appendix A) were shared with referring clinicians, enabling them to identify and pre-screen suitable candidates effectively. These partnerships not only expanded the trial's geographic and clinical reach but also reduced the likelihood of unnecessary disqualifications by aligning screening processes with trial requirements. Referring clinicians played a pivotal role in streamlining the recruitment pipeline by ensuring that only candidates meeting the eligibility criteria were referred for further assessment.

Additionally, the trial team actively engaged with national and regional SCI organizations, including patient support groups and rehabilitation centers, to enhance awareness and outreach. These organizations proved instrumental in connecting with potential participants and disseminating trial information through diverse channels, including print media, social platforms, and community events (Appendix B). By providing a trusted conduit for communication, these partnerships amplified the trial's visibility within the SCI community and fostered a sense of inclusion and trust.

Together, these strategies effectively addressed the challenge of a limited candidate pool by broadening the recruitment network and ensuring a more focused and efficient screening process. This collaborative, multi-channel approach underscores the importance of leveraging clinical and community partnerships to overcome recruitment barriers in trials involving rare and complex conditions like chronic motor complete SCI.

2.2. Mitigating Patient Skepticism and Fear of Invasive Procedures

Patients may exhibit significant hesitancy toward participating in clinical trials involving spinal cord stimulation (SCS) due to concerns about the invasive nature of the procedure and its long-term management demands. These apprehensions can be further compounded by the off-label use of SCS, which may amplify doubts about its safety and efficacy. Recruiting patients for neurorestorative clinical trials has historically been challenging—not only in SCI but across conditions involving central nervous system (CNS) damage—primarily due to the long-standing belief that functional recovery in CNS injuries is impossible [10]. This widespread skepticism has deeply influenced both patients and clinicians' attitudes. However, the field has seen rapid and consistent progress over the years [10,11].

To address these challenges, the RESTORES trial team implemented a comprehensive recruitment strategy centered on robust pre-surgical counselling designed to educate both patients and their caregivers. Each potential participant engaged in a minimum of three personalized, one-on-one counselling sessions with the principal investigator (PI) before enrolment. These sessions provided detailed insights into the SCS procedure, including its mechanism of action, safety profile, and outcomes from prior research. Importantly, patients were informed about global advances in neurorestoratology, including results from high-profile studies like E-STAND [12], ONWARD [13], and Up-LIFT [13], as well as yearly progress captured in the 2022 and 2023 Yearbooks of Neurorestoratology—discussing advances in neuromodulation, neurostimulation, and neurorestorative therapy [10,11]. Highlighting such emerging evidence helped counteract prior perceptions and offer patients tangible proof of ongoing clinical successes, which positively influenced their willingness to participate. Additionally, the discussions offered a platform for participants and their families to voice individual concerns, clarify uncertainties, and understand the potential risks, benefits, and expected outcomes of this study. By fostering open communication, the counselling sessions aimed to dispel misconceptions, alleviate fears, and build trust in the research team and procedures, thereby empowering informed decision-making.

Recognizing the significance of rigorous oversight in first-in-man trials, the study team established a data safety monitoring board (DSMB). This independent body, comprising a chairperson and four voting members unaffiliated with the trial's conduct, played

a pivotal role in addressing patient skepticism and ensuring this study's integrity. The DSMB's responsibilities included reviewing cumulative data to evaluate participant safety, assessing the trial's scientific validity, and monitoring compliance with ethical standards. Before enrolling each participant, the DSMB meticulously examined their eligibility and analyzed safety data from previous participants to ensure continuous risk assessment.

By implementing an independent oversight mechanism, the DSMB not only reduced concerns about potential bias or oversight of adverse events but also bolstered this study's credibility. Its proactive involvement reassured participants and caregivers that their safety and well-being were paramount. This commitment to transparency and accountability reinforced participant confidence, contributing significantly to overcoming recruitment barriers and fostering acceptance of this innovative, invasive therapeutic intervention.

2.3. Reducing Potential Medical Complications

Mechanical unloading, a frequent consequence of paralysis, induces rapid and severe osteoporosis in individuals with spinal cord injury (SCI), significantly increasing their susceptibility to fractures. This condition is primarily driven by the elevated expression of sclerostin by osteocytes, which inhibits bone formation, alongside indirect stimulation of bone resorption [14,15]. These effects are exacerbated by the loss of weight-bearing activities and hormonal dysregulation, further accelerating bone density loss [14,15]. Addressing this critical issue was essential for the RESTORES trial, as the rehabilitation regimen involved repetitive physical activities that could pose significant fracture risks in participants with compromised bone health.

To mitigate these risks, stringent screening protocols were implemented to exclude individuals with severe osteoporosis, defined by a T-score less than -2.5. Potential participants underwent comprehensive bone mass density (BMD) evaluations to ensure they met the safety criteria. For individuals with BMD scores indicating osteopenia (T-score between -1 and -2.4), additional assessments were conducted to confirm their suitability for participation, ensuring their bone health was sufficient to tolerate the rehabilitation program without undue risk.

The trial's rehabilitation program incorporated a combination of advanced technologies and conventional physiotherapy to maximize therapeutic outcomes while prioritizing patient safety. A central component was the use of a wearable robotic exoskeleton, the EksoGT (Ekso Bionics, Richmond, CA, USA). Each participant was custom-fitted with the "robotic" exoskeleton, which facilitated supported, repetitive movements to enhance motor function and improve range of motion "of the lower limb". This was complemented by conventional physiotherapy, which included targeted stretching and strengthening exercises for the trunk and extremities. Supported standing using a standing frame was gradually introduced to improve verticalization tolerance, while electric arm and leg cycling promoted cardiovascular health and joint mobility.

This comprehensive and carefully tailored approach balanced the need for rigorous rehabilitation with the imperative of safeguarding participant well-being. By proactively addressing osteoporosis-related risks, the trial ensured that participants could safely engage in the demanding rehabilitation activities, maximizing the potential for functional improvements while minimizing the likelihood of adverse outcomes. This strategy underscores the importance of integrating thorough pre-participation assessments and individualized care in clinical trials targeting populations with complex medical needs like chronic SCI.

2.4. Overcoming Geographical and Logistical Barrier

The trial's rigorous daily rehabilitation schedule, spanning seven months and involving frequent follow-up visits, posed significant logistical challenges for participants, particularly those with limited mobility, financial constraints, or both. To ensure accessibility and minimize barriers to participation, the study team implemented a range of support measures tailored to address these challenges comprehensively.

Singapore's well-developed public transportation infrastructure, including buses, the Mass Rapid Transit (MRT) system, and taxis, provided a reliable, affordable, and accessible means for participants to travel to the trial site. These transport options ensured that even participants residing outside central areas could maintain their rehabilitation schedules with relative ease. To further alleviate financial strain, participants were reimbursed for travel expenses, regardless of whether they used public transport, taxis, or private vehicles. This proactive measure ensured that transportation costs did not discourage individuals from participating, particularly those from lower-income households.

In addition to leveraging public transport, the trial team established robust logistical support systems to enhance participant accessibility. Detailed transport guides were provided to help participants navigate their travel routes efficiently. Flexibility in scheduling rehabilitation sessions was also introduced, accommodating individual preferences and personal commitments. For participants facing severe mobility challenges, specialized arrangements were made, such as coordinating with transport services designed to assist individuals with disabilities. These services included wheelchair-accessible vehicles and door-to-door pick-up and drop-off options, significantly easing the logistical burden for participants with higher support needs.

By implementing these inclusive and participant-centric strategies, the trial team successfully expanded accessibility, enabling a more diverse range of participants to engage in this study. These measures not only facilitated adherence to the demanding rehabilitation protocol but also fostered a supportive and equitable environment, underscoring the team's commitment to overcoming logistical barriers and ensuring the trial's success. This approach highlights the critical role of logistical planning in clinical trials, particularly those involving complex and resource-intensive interventions, and serves as a model for future studies aiming to enhance accessibility and participant engagement.

2.5. Addressing Emotional and Psychological Barrier

Patients with chronic spinal cord injuries (SCIs) often contend with profound emotional and psychological challenges, including depression, anxiety, and a pervasive fear of disappointment [16]. These issues can significantly diminish their motivation to participate in clinical trials, particularly those involving experimental interventions like spinal cord stimulation (SCS). Additionally, the emotional burden of balancing high hopes with the inherent uncertainties of such trials can deter potential participants [17,18].

To address these challenges, the RESTORES trial team implemented a robust pre-enrolment assessment process to evaluate each candidate's mental and emotional well-being. This process included administering the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) assessment and a Quality of Life (QoL) questionnaire. These tools helped identify psychological issues such as depression, anxiety, or emotional instability that could interfere with trial engagement. Beyond clinical assessments, in-depth discussions with potential participants focused on understanding their expectations, coping mechanisms, and mental resilience, which included sharing examples from contemporary international trials [12,13,19] and yearly clinical achievements, as mentioned above [10,11]. These trials involve pharmacologic, neuromodulation, and rehabilitative combinations, underscoring global recognition of the urgent need for functional recovery options in SCI.

Incorporating such developments during counselling may improve decision-making and address therapeutic uncertainties. These conversations ensured that candidates were emotionally prepared to handle the physical and psychological demands of the trial, fostering a foundation for successful participation.

Realistic and transparent communication formed a cornerstone of the recruitment process [16]. The trial team emphasized the experimental nature of the intervention, clearly outlining potential outcomes, risks, and limitations. By setting achievable expectations, participants were better equipped to cope with both successes and setbacks, reducing the emotional toll of unmet hopes [6,7]. Regular progress updates, including videos showcasing functional improvements, were shared with participants to maintain motivation, reinforce their commitment, and instill a sense of accomplishment.

Recognizing the critical role of social support, the trial encouraged family and caregiver involvement throughout the process [20]. Families or close friends were invited to participate in trial-related discussions, where they received detailed information about the intervention, potential risks, and expected outcomes. This inclusive approach not only strengthened participants' emotional and logistical support systems but also empowered family members to actively contribute to the rehabilitation journey. By fostering a collaborative and transparent environment, the trial team successfully addressed participants' psychological concerns, ensuring a positive and supportive experience for both patients and their families [20,21].

2.6. Study Dedicated Clinical Research Coordinator (CRC)

A dedicated CRC played a pivotal role in ensuring the success of trial recruitment and managing the ethical and regulatory aspects of this study. The CRC's responsibility included screening potential participants, ensuring they met this study's eligibility criteria and coordinating their enrolment. Beyond these recruitment duties, the CRC also oversaw the trial's compliance with institutional review board (IRB)-approved protocols, and ensured adherence to patient confidentiality regulations, such as the Personal Data Protection Act (PDPA) [22]. They also managed all necessary documentation to maintain the trial's integrity [22]. The CRC coordinated communication between the research team and the IRB, keeping study status regularly updated, and ensuring that any amendments to the study protocol or forms were promptly reviewed and approved. Furthermore, the CRC prepared the site for potential audits, ensuring that the investigator's site files were meticulously maintained and up to date [22,23]. By managing these regulatory and administrative responsibilities, the CRC ensured this study remained in compliance with ethical standards and regulatory requirements, while also guaranteeing the reliability and validity of the data collected. In a complex study like this, where multiple disciplines are involved with regulatory and ethical considerations to manage, a CRC acts as a linchpin, connecting various elements of the study—from patient recruitment and consent to data collection and reporting—ensuring that the research is conducted smoothly with credible and ethically sound study outcomes [22,23].

3. Results

During the recruitment period, 115 patients were screened for the RESTORES trial, as shown in Figure 1. Of these, 100 were deemed ineligible due to having incomplete spinal cord injuries (SCI), which did not meet the trial's strict inclusion criteria. Among the remaining candidates, five patients declined participation, citing apprehensions about the intensive nature of the trial, which required a demanding rehabilitation schedule and invasive procedures. Additionally, three candidates were excluded due to severe osteoporosis, a condition that posed a significant risk for fractures during the rehabilitation regimen.

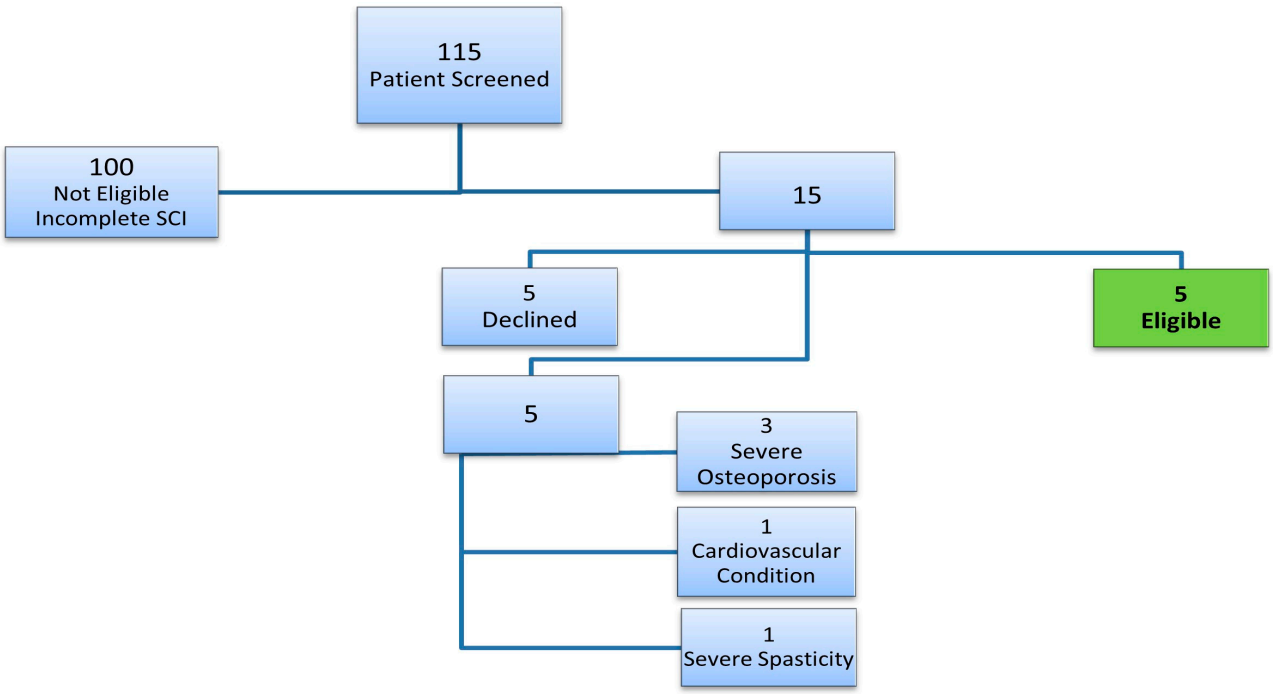


Figure 1. Patient Screening. Total number of patients screened, reasons for patient exclusion, and the final number of eligible patients.

Two more patients were excluded based on specific criteria outlined in Appendix A—one due to a severe cardiovascular condition and the other because of significant spasticity that would interfere with the therapy protocol. Beyond medical factors, the participants' level of determination and commitment emerged as a critical consideration. The trial required dedication to an intensive and prolonged therapy regimen, leading to the exclusion of two individuals who demonstrated insufficient motivation to adhere to the schedule.

Geographical and logistical challenges also impacted recruitment. Three patients residing outside Singapore expressed interest but were ultimately unable to participate due to the long-term commitment required and the need for frequent visits to the trial site. These logistical barriers, coupled with the trial's rigorous demands, added to the overall recruitment challenges.

Collectively, these factors underscore the complexities of recruiting suitable candidates for a high-intensity, long-term clinical trial. They highlight the importance of addressing medical, logistical, and psychological barriers to participation, as well as the critical need for robust screening processes to ensure that participants are both medically eligible and fully prepared to commit to the demands of a study.

Recruitment for the third participant in our study presented significant challenges following the successful enrolment of the first two patients as shown in Figure 2. One potential participant withdrew after further consideration, citing personal reservations, while another promising candidate was disqualified due to a diagnosis of spondylodiscitis. Despite these setbacks, and after multiple screenings, we were able to recruit a final participant who met all inclusion and exclusion criteria.

Interestingly, the recruitment of the third participant was notably influenced by the encouragement of the first participant, underscoring the importance of peer support within the spinal cord injury (SCI) community. Both individuals were active members of an SCI peer support group, which fostered a strong sense of camaraderie and shared experience. The first participant, having achieved remarkable functional improvements in mobility and independence during the trial, became an advocate for this study. He shared

detailed accounts of his experiences, including the procedural process and observed outcomes, which helped to address the concerns and build trust in the trial.

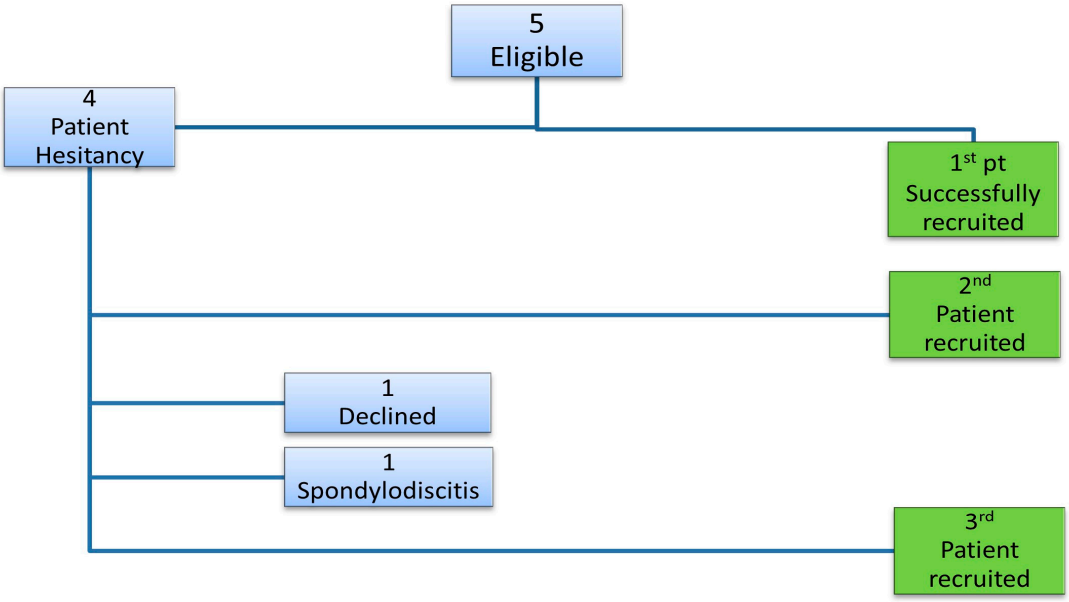


Figure 2. Patient selection. Recruitment process for the 5 eligible patients.

Motivated by the firsthand testimonial and the potential for similar benefits, the third participant chose to enroll in this study. This case highlights the significant role that peer influence and personal narratives can play in enhancing recruitment and fostering confidence in experimental treatments within patient communities.

4. Discussion

Spinal cord injury (SCI) is a significant global public health concern, affecting individuals across all ages and demographics [24]. While precise global prevalence rates are challenging to determine due to inconsistencies in data collection and reporting, estimates suggest that approximately 15 million people worldwide are living with SCI [25]. In Singapore, the annual incidence of SCI is reported to be 23 cases per million population [9,26], with a substantial proportion of cases attributed to traffic accidents [27]. This reflects global trends, where road traffic injuries are a leading cause of SCI [24,25]. A systematic review of SCI incidence in Asia reveals a wide variation, ranging from 10.8 to 22.7 cases per million population, underscoring the need for standardized data collection and reporting practices across the region [26].

The field of spinal cord injury (SCI) research is undergoing a transformative period, with emerging therapies and technologies offering new prospects for improved patient outcomes. Among these advancements, spinal cord stimulation (SCS) has emerged as one of the most promising interventions. Recent studies have demonstrated the potential of SCS to facilitate the restoration of neuronal networks and promote neurological recovery [17,19,28]. The RESTORES study represents a significant milestone in this field as the first-in-man trial conducted in Singapore. Designed as a feasibility study, RESTORES operated with limited resources and a small sample size, recruiting three participants to evaluate the project's viability. This study aimed to systematically assess the technical feasibility of SCS, establish a standardized workflow encompassing all stages from patient recruitment to trial completion, and identify potential risks associated with the intervention.

Findings from this preliminary investigation provide critical insights to inform future efforts in refining and scaling this innovative therapeutic approach, laying the groundwork for broader clinical application and advancing the field of SCI rehabilitation.

4.1. Recruitment Barriers and Strategies

Recruitment for the RESTORES study posed several challenges, underscoring the complexity of enrolling suitable candidates for an intensive and pioneering trial. Key factors contributing to the exclusion of potential participants included the limited patient pool, skepticism about experimental treatments, stringent eligibility criteria, geographical and logistical barriers, and emotional and psychological concerns.

During initial consultations, emphasizing the importance of commitment proved critical in identifying motivated candidates who were likely to adhere to the rigorous therapy regimen [29]. This approach ensured that enrolled participants were well prepared for the demands of the trial.

The recruitment process revealed notable differences between self-referrals and professional referrals. Professional referrals, particularly those from physicians and physiotherapists, often yielded participants with higher eligibility consistency. This is likely attributable to the referrers' comprehensive understanding of both this study's inclusion and exclusion criteria and the patients' medical conditions. Conversely, self-referred participants demonstrated greater self-motivation and higher levels of trust in the innovative nature of the intervention.

Collaboration with national and regional SCI organizations, including patient support groups and rehabilitation centers, further facilitated recruitment efforts by increasing awareness of this study. This strategy not only expanded the recruitment pool but also enabled connections with highly motivated individuals, such as members of SCI peer support groups. For instance, the recruitment of the third participant was influenced by the encouragement of the first participant, who had experienced significant functional improvements through the trial. By sharing his personal experience and insights, he alleviated the third participant's concerns, built trust, and ultimately motivated her enrolment in this study.

Recent commentary by Scheuren et al. has urged the SCI field to embrace adaptive design features and pre-specified sub-group analyses to reduce ethical burden while preserving scientific validity [30]. While our trial employed strict eligibility criteria and pre-implantation screening, future studies may benefit from stratification models and registries to accelerate recruitment without compromising rigor.

These findings offer valuable insights for refining recruitment strategies, emphasizing the importance of leveraging both professional referrals and peer advocacy within the SCI community. Furthermore, the results underscore the critical role of personal testimonials and shared experiences in fostering patient confidence and participation in novel therapeutic trials.

4.2. Family Support

Spinal cord injury (SCI) is a life-altering condition that significantly diminishes an individual's independence and quality of life. In most cases, caregiving responsibilities are undertaken by family members, often driven by social or economic factor [31]. Research has consistently highlighted the vital role of family support in the lives of individuals with SCI, with studies demonstrating that the absence of family caregivers increases the likelihood of patients being excluded from research studies [31]. Acknowledging this, the RESTORES study team actively encouraged the involvement of family members or close friends throughout this study. Caregivers were invited to participate in trial-related discussions, spanning from the pre-enrolment phase to study completion, fostering a sense

of shared responsibility and support. This approach enabled caregivers to play an active role in the participant's rehabilitation journey [20,21].

The RESTORES trial involved an intensive rehabilitation protocol, requiring a total commitment of seven months. Participants engaged in two sessions per week for one month prior to spinal cord stimulator (SCS) implantation and five sessions per week for six months post-implantation. The demanding schedule occasionally resulted in physical and mental fatigue, as well as fluctuations in mood among participants. While the multidisciplinary team provided professional support, the involvement of family members remained a cornerstone of care throughout the trial. Family caregivers played a critical role, not only by assisting participants with rehabilitation exercises at home but also by offering emotional stability, motivation, and a sense of belonging [18,32]. The study team prioritized transparent communication with participants and their families, providing regular updates on trial goals, including video documentation of functional improvements. This approach helped maintain engagement and optimism among participants [6,7]. The commitment of family members proved invaluable in sustaining participants' motivation and adherence to the rehabilitation process. Their support was instrumental in facilitating recovery and ensuring that participants remained engaged and resilient throughout the trial [18].

Understanding that rehabilitation is not merely supportive but is an essential, synergistic partner in SCS-based recovery is crucial. As Boccia et al. noted, rehabilitation must be both personalized and accessible to meet the long-term needs of SCI patients [33]. Our approach integrates cost-effective, technology-supported rehabilitation to maximize patient outcomes, which in turn reduces the burden on both patients and their families.

4.3. Ethical Considerations

Ethical considerations were integral to every aspect of the trial, guided by the core principles of medical ethics: autonomy, beneficence, non-maleficence, and justice [34,35].

Autonomy was upheld by ensuring participants provided informed consent after a thorough understanding of the risks and benefits of this study [34,36]. Trial participants in our study underwent a comprehensive process that included counselling sessions with the PI prior to obtaining consent. This included detailed conversations about the study procedures, potential outcomes, and any associated risk. This approach ensured that patients' decisions were based on their complete understanding of this study.

Beneficence was reflected in the trial design, which aimed to maximize potential benefits, such as improving neurological function through innovative therapies [36]. On top of that, the team ensured that participants were emotionally healthy and had strong family support to assist them throughout the trial before recruiting them.

Non-maleficence was prioritized by meticulously assessing risks, particularly given the invasive nature of spinal cord stimulation (SCS), and by maintaining participant safety as the trial's foremost concern [34]. The strict eligibility criteria (Appendix A) established in our study were crucial in upholding the principle of non-maleficence, as we excluded patients suffering from severe spasticity and osteoporosis, safeguarding them against potential deterioration of their conditions.

Justice was addressed by promoting equitable access, including providing travel support and minimizing financial barriers, ensuring that all eligible participants, regardless of socioeconomic background, had an equal opportunity to participate [34,36].

The clinical research coordinator (CRC) played a pivotal role in managing these ethical and logistical challenges. Acting as the primary liaison between participants, the clinical team, and regulatory bodies, the CRC ensured that participants understood the trial procedures, addressed their concerns, and coordinated essential logistics, such as travel and follow-up care. Furthermore, the CRC maintained compliance with institutional review board (IRB) protocols, managed patient confidentiality, and oversaw the ethical and regulatory aspects of this study. By managing these critical responsibilities, the CRC ensured that recruitment and trial processes proceeded smoothly, ethically, and with a steadfast focus on participant welfare and this study's integrity.

5. Conclusions

In conclusion, the RESTORES trial successfully addressed multiple recruitment barriers through a combination of strategic outreach, patient education, logistical support, psychological care, and the dedicated efforts of a CRC. These strategies were essential for overcoming the limited patient pool, managing patient apprehensions, navigating eligibility criteria, and addressing logistical and emotional challenges. This study highlights the necessity of innovative approaches and multidisciplinary collaboration in addressing the complex needs of SCI patients. The insights gained from this trial will inform future research and clinical practices, aiming to enhance therapeutic strategies and improve the overall quality of life for individuals living with chronic motor complete SCI.

Author Contributions: F.M. and K.R.W. provided all oversight for this manuscript. K.R.W. provided all oversight for this study. K.R.W., W.H.N., R.X.J.K., S.K.W., Z.Y.V.N. and W.L.L. designed this study and implemented the strategies for recruitment challenges together with F.M., K.R.W., S.K.W., Z.Y.V.N., W.L.L. and M.W.P. provided perioperative rehabilitation and aided patients with logistical and emotional support. All authors including S.E.S., R.Q.S., B.P. and K.S. provided critical feedback for the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Singhealth Centralised Institutional Review Board, Singapore (approval code 2022-2496, approved on 2 October 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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Conflicts of Interest: The authors declare no conflicts of interest. The funder of this study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Appendix A

Eligibility Criteria

Description

• Inclusion Criteria

For inclusion in the study, the potential patient has to fulfil all of the following criteria:

1. 21 years old and older
2. Chronic (greater than one year) motor complete (AIS classification A or B) SCI
3. Spinal injury between the levels of Thoracic 2 (T2) to Lumbar 1 (L1)
4. Segmental reflexes that remain functional below the level of lesion
5. Able to perform the perioperative rehabilitation program as judged by the research team

    - Exclusion Criteria

Potential patients will be excluded from the trial if they fulfil any of the following criteria:

1. Significant medical co-morbidities that would significantly increase the risk of the operation
2. Severe dysautonomia with systolic blood pressure fluctuation less than 50 or more than 200mmHg on tilt table testing
3. Painful musculoskeletal dysfunction, contractures, unhealed fractures, pressure sores, severe spasticity, and osteoporosis
4. Significant psychological issues or ongoing drug abuse
5. Pregnancy and lactating patients
6. Progressive spinal cord disease

Figure A1. RESTORES study's inclusion/exclusion criteria [37].

Appendix B

Paralysed men can walk again after spinal implant

Judith Tan
Correspondent

Mr Sam Subian, 49, was a competitive jockey for 25 years until his horse Silver Spoon stumbled during training in June 2017, flinging him onto the track.

"Silver Spoon died and I fractured my spine. I could not sense anything below my chest. I was told I would never stand or walk again," Mr Sam said.

It took him a few years to come to terms with not being able to walk, let alone compete, and he was worried about who would care for his mother.

But for the past seven months, Mr Sam has been able to walk unassisted, thanks to an implant that helps overcome the damage to the nerve pathways in his spinal cord – and lots of hard work.

He was the first of three participants in a new clinical trial here, called Restores (restoration of rehabilitative function with epidural spinal stimulation), which may spell hope for people who would otherwise never walk again.

Spinal cord damage disrupts the transmission of electric impulses or signals that control movement and sensation from the brain to parts of the body like the arms and legs, depending on where the damage is. These signals travel over nerve pathways.

The procedure involves implanting a spinal cord stimulator – an electrode powered by a battery pack inserted into the lower back and connected to the covering of the spinal cord below the damaged area.

"The aim of the trial is to bridge the damaged part of the spinal cord and boost signals from the brain to the muscles by tapping residual pathways that are still viable," said neurosurgeon Wan Kai Rui from the National Neuroscience Institute (NNI).

The stronger signals can stimulate a person to walk again.

After the implant operation, participants undergo advanced robotic rehabilitation.

The researchers study how this helps improve nerve and muscle functions in patients paralysed from the chest down.

The procedure is the first of its kind in the region, and is being trialled by NNI, Tan Tock Seng Hospital (TTSH) and the Agency for Science, Technology and Research, with grants from the National Medical Research Council and the Ng Teng Fong Healthcare Innovation Programme.

The second participant is financial adviser Asyraf Ghazali, 28. He was in a road accident in 2018 that severed his spine and left him paralysed from the chest down.

"I was in the prime of my life when it happened. Like Sam, I made up my mind to move on with life, but I continuously looked for treatments to help me walk again," he said.

He received his implant in March, a month after Mr Sam had his operation. The third, a woman, will get an electrode implanted in January 2024.

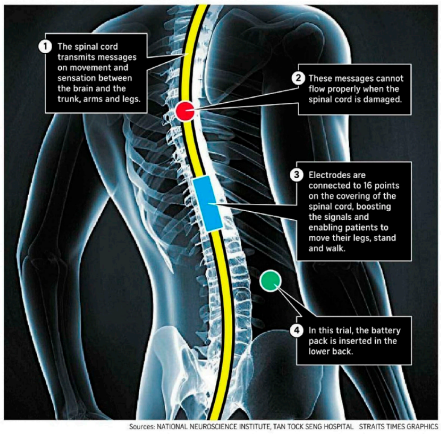
Dr Wan said TTSH and NNI in total treat about 100 new cases of spinal cord injury a year, and about 95 per cent of "motor complete" spinal cord injury patients –

CONTINUED ON PAGE A2



Mr Sam Subian (left), being assisted by principal physiotherapist Phua Min Wee, and Mr Asyraf Ghazali (right), being assisted by senior principal physiotherapist Wee Seng Kwee, relearning how to walk at the Centre for Advanced Rehabilitation Therapeutics at Tan Tock Seng Hospital on Nov 28. ST PHOTO: LIM YAOHUI

How the spinal implant works



Sources: NATIONAL NEUROSCIENCE INSTITUTE, TAN TOCK SENG HOSPITAL STRAITS TIMES GRAPHICS

Phase two of trial to proceed with 15 patients

FROM A1

those with no sensation below the site of injury – have no neurological improvement five years after their injury.

A month after their surgery, both Mr Sam and Mr Asyraf were put through intense rehabilitation to get them to stand on their own and walk with a walking frame.

They were fitted into a robotic exoskeleton suit to simulate walking, increase the number of repeat steps taken and strengthen their trunk and leg muscles.

Senior principal physiotherapist at TTSH Wee Seng Kwee said motor imagery is also used.

"This is to have them imagine a movement, despite not being able to actively move. With mind over matter, the patients could eventually move parts of their legs that they could not before," said consultant Valerie Ng.

But while they can move, they do not feel themselves moving.

"I was sceptical at first because prior to this, I suffered spasms. When the (medical) team told me that my toes were moving, I did not believe them and put it down to spasms until I started moving my knee," Mr Asyraf said.

The men progressed quickly, moving from the use of the robotic exoskeleton to walking with a ceiling hoist in slightly over a month, and then to daily physiotherapy sessions overground in just seven months.

The results have surpassed what other similar programmes have achieved, said Dr Wan.

One programme in Texas, in the United States, carried out conventional rehabilitation twice a day for 1½ years to 2½ years "to achieve what we did in six months", she said.

A recent one carried out in Switzerland had its own implants created, "which limits scalability and accessibility", Dr Wan added.

At Restores, apart from using pre-existing implants that are easily available, the team also came up with a rehabilitation programme and programming recommendations that allow for efficient improvement.

The team will be moving into phase two of the trial with about 15 patients with spinal cord injury.

"We will also be looking at those with paralysis from the neck down. We want to see how such electrode stimulation can help with the movement in their arms," Dr Wan said.

Mr Sam, a sports adviser at sports goods retailer Decathlon, is a fan of the 1970s television series The Six Million Dollar Man, about a former astronaut who was "rebuilt" with bionic implants after a test flight accident.

"With the electrode and battery pack in me to help me walk, I feel like I'm a One Million Dollar Man."

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Figure A2. *Cont.*



Percubaan TTSH, Institut Neurosains, beri harapan pesakit lumpuh kembali 'berjalan'

KEMBALI BERJALAN: Dua pesakit lumpuh, Encik Sam Subian dan Encik Asyraf Ghazali (dua dan tiga dari kiri), kini boleh 'berjalan' dengan penyeliaan selepas jalani satu percubaan oleh Hospital Tan Tock Seng dan Institut Neurosains Kebangsaan. – Foto BH oleh SHAFIQ APANDI

► HARITH MUSTAFFA
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Dua lelaki lumpuh dari bawah dada sejak selurang-kurangnya lima tahun lalu dek kemalangan, kini berupaya 'berjalan' selepas menjalani satu percubaan bermatlamat menggalakkan fungsi penggerakan kepada pesakit yang hilang sepenuhnya fungsi pergerakan ekoran kecederaan pada kord tulang belakang (SCI).

Encik Sam Subian, 49 tahun, dan Encik Asyraf Ghazali, 28 tahun, telah menyertai percubaan dijalankan bersama Institut Neurosains Kebangsaan (NNI), Hospital Tan Tock Seng (TTSH) dan Agensi bagi Sains, Teknologi dan Penyelidikan (A * STAR) itu sejak awal tahun ini.

Kini, mereka berupaya menggerakkan jari kaki, bulu lali, serta bangun dari kerusi dan berjalan dengan penyeliaan dengan bantuan satu implan yang dipasang di tulang belakang.

Percubaan dinamakan Pemulihan Fungsi Rehabilitasi menerusi Perangsang Epidural Tulang Belakang atau 'Restores', mula merekrut peserta sejak Disember 2022.

Ia melibatkan penggunaan sejenis alat elektrod – atau pengalir elektrik – yang dipasang di permukaan tulang belakang peserta menerusi pembedahan yang kemudian diikuti rawatan pemulihan berlangsung beberapa bulan.

Saiz alat itu, persis jari kecil, berfungsi memberangsangkan isyarat daripada otak dan menyalurkannya kepada kord tulang belakang pesakit supaya mereka dapat menggerakkan bahagian tubuh yang hilang keupayaan itu.

Hasil fasa pertama percubaan itu – yang disokong geran Majlis Kajian Perubatan Nasional (NMRC) dan Program Inovasi Kesihatan Ng Teng Fong – diumumkan satu pasukan terdiri daripada pakar TTSH, NNI dan A * STAR dalam satu sidang akhbar pada Selasa.

Encik Asyraf, peserta kedua percubaan itu, yang lumpuh selama lima tahun, mula berjalan dengan bantuan penyeliaan pada Ogos.

Peserta pertama, Encik Sam, yang lumpuh selama enam tahun selepas terjatuh ketika mengendalikan seekor kuda, menyertai percubaan itu pada Disember 2022 dan mula berjalan dengan penyeliaan pada September 2023.

Percubaan Restores itu melibatkan peserta yang diklasifikasikan gred Asia 'A' iaitu pesakit yang mengalami kehilangan keupayaan dan deria di bawah bahagian tubuh yang mengalami kecederaan.

Percubaan itu bermula dengan proses prahabilitasi – pesakit diperlukan jalani tempi dua kali seminggu dalam tempoh sebulan melibatkan sut bantuan pergerakan atau 'exoskeleton', dan fisioterapi.

Kemudian pesakit akan jalani pembedahan bagi memasukkan alat elektrod itu di tulang belakang mereka.

Selepas berehat sebulan pasca pembedahan, pesakit akan jalani latihan pemulihan pergerakan sekitar lima hingga tujuh bulan, meliputkan latihan menguatkan otot, pergerakan asas seperti duduk dan berdiri, dan berjalan.

Semasa menjalankan latihan pemulihan itu, para doktor akan hidupkan alat elektrod itu menerusi satu peranti digital berbentuk tablet, yang boleh mengubah kuasa alat itu menurut kesesuaian pesakit berdasarkan tugas atau pergerakan yang hendak dilakukan mereka.

Sedang itu berlaku, penaiti itu akan menjejak pergerakan peserta menerusi kaedah komputer dan akan mempertingkat lagi kaedah itu menerusi teknologi kecerdasan buatan atau AI.

Dr Wan Kai Rui, penyelidik utama percubaan Restores berkata, matlamat lanjut pasukannya adalah untuk berusaha mencapai pemulihan deria dan beliau sedang bekerjasama dengan beberapa rakan industri untuk berbuat demikian.

"Pada tahap ini kami telah mencapai pemulihan pergerakan, namun pemulihan deria juga penting sebab meskipun mereka (peserta) boleh berjalan, ia tidak selamat sepenuh hati mereka kerana mereka tidak berupaya rasa lantai dan permukaannya semasa berjalan," katanya.

通过电极植入及物理治疗

本地新研究助脊髓受损瘫痪者重新站立

研究包含三个阶段：病患在植入电极前，进行一个月的术前康复；随后，团队会将电极植入病患骨髓中，刺激神经线以搭建大脑与脊髓的"桥梁"；最后，病患会进行为期七个月的个人化康复治疗。

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瘫痪者重新站立和行走不再是幻想。本地新研究让脊髓受创的病患重获动作技能，开启未来更多希望。两名下半身瘫痪的病患今年初参与本地研究团队展开的研究，过程结合电极植入及物理治疗，成功在脊髓受损重创后首次站立。

来自国立脑神经医学院、陈笃生医院以及新加坡科技研究局的研究团队从去年12月开始招募脊椎损伤病患，展开脊髓神经刺激疗法研究。

研究包含三个阶段：病患在植入电极前，进行一个月的术前康复（prehabilitation）；随后，团队会将电极植入病患脊髓中，刺激病患神经线，以搭建大脑与脊髓的"桥梁"；最后，病患会在术后一个月，进行为期七个月的个人化康复治疗。

国立脑神经医学院脑神经外科高级顾问医生伍伟豪教授说，植入手术时长约两小时至四小时，与其他脊髓手术比起来，也相当安全，受感染出现并发症等的概率仅约5%。

病患术后的康复计划着重于三种不同训练，即运动想象（motor imagery）、核心训练及利用机械外骨骼（exoskeleton）模拟步行、唤起肌肉记忆。为让康复过程有效且有趣，团队也融入了虚拟实境游戏，特别的"马术治疗"（hippotherapy），以及辅助性的步行运动等疗法。

团队一共招募了三名因脊髓受损，导致胸部以下瘫痪的病患。当中两名病患山姆（Sam Bin Subian，49岁）与阿斯拉夫（Asyraf Bin Ghazali，28岁）已顺利完成治疗研究，而第三名病患明年初开始接受治疗，预计在第三季结束。

两名病患在完成第一个月的康复训练后，可独立完成从坐到站的动作，而在七个月的康复疗程结束后，可在监护下行走。

曾是全职警马骑士的山姆因六年前不幸坠马，导致脊髓严重损伤，胸部以下完全瘫痪。

"我原来对已经骑在医院了，根本不知道发生了什么事。我很热爱我的工作，所以在得知我的胸部以下都瘫痪时，实在难以接受。生活上很多简单的事情我也都做不了，就连上厕所也需要别人帮忙。"

他说："我有尝试过其他的疗法，希望能对情况有所改善，但都无济于事。这也是为什么我会毫不犹豫地参与这项研究。"

山姆接下来的目标是在没有支架辅助的情况下独自站立，也希望自己的经验能给其他人带来希望。

阿斯拉夫则在2018年的电单车事故中脊髓损伤，造成下半身瘫痪，改变了他人生的轨迹。

他说，意外发生时他在服兵役，对年轻且身体健壮的他来说，半身瘫痪是不可想象的情景。

加入研究前，他也曾试图找寻一些可助他康复的治疗，但毫无收获。"我其实找到泰国一个提供植入手术的地方，但我的担忧程度并不亚于接受的治疗费用内，申请被拒绝了。在那之后，我就没有再另寻他法，选择接受自己余生瘫痪的事实。"

阿斯拉夫指出，除了行动方面有所进展，尿失禁的情况也在参与治疗后改善，生活品质大大提高。

病患恢复感觉。"感觉非常重要，虽然他们现在能步行，但安全性不高，若感觉不到脚下的地面，有被绊倒或摔倒的可能。"

她指出，下一个阶段的研究预计将招募约15名病患，也将接受脊髓受损级别较高、颈部以下瘫痪的病患，以帮助他们恢复手部的动作能力，提高生活品质。

无法想象自己能再次站立的山姆（左三）和阿斯拉夫（右二），在完成了七个月的康复治疗后已能靠辅助工具独自站立和行走。（特约报道）

Figure A2. Singapore's local newspaper, 'The Straits Times' article on the RESTORES study [38]. The same article was published, as seen below, in both the local Malay-language newspaper, Berita Harian, [39] and Chinese-language newspaper, Lianhe Zaobao [40].

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