Section 1 **Technology of neurorehabilitation: outcome measurement and diagnostic technology**

Chapter 1

Clinical trials in neurorehabilitation

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Introduction

Clinical trials in neurological rehabilitation gradually acquire evidence for well-defined interventions that may lessen clinically important impairments and disability and increase activity, participation, and health-related quality of life. The research interventions tested include physical, cognitive, adaptive, behavioral, and psychosocial training, as well as pharmacological manipulations, external electrical stimulation to augment Hebbian learning, and biological strategies for neural repair. No one set of procedures for pilot studies and randomized clinical trials (RCT) will be applicable to the diverse needs and potential therapies for patients. Trial designs are influenced strongly by the heterogeneous range of disease pathologies; the types, combinations, and severity of impairments; and by patient preferences for outcomes. The results of many trials have been described in other chapters. Here we look at more general aspects of research designs – types of clinical trials, the progressive staging of trials, enrichment strategies to improve trial designs, potential confounders in gathering evidence, and the need for collaboration.

Phases of clinical trials

The U.S. Food and Drug Administration (FDA) examines clinical trials in medicine in three phases. *Phase I* involves a relatively high risk or novel intervention given to a small number of healthy or affected subjects. Establishing safety and examining responsiveness are the primary goals. *Phase II* follows Phase I and builds upon knowledge of risks. More subjects are involved. Safety and potential efficacy are studied. The effects of different dosages of a medication or intensity of an intervention are determined, along with the best research methodology and outcome measures, in preparation for Phase III. *Phase III* more rigorously assesses the potential for efficacy of the intervention by a randomized trial with blinded outcomes, comparing the new intervention to a standard one or to a placebo. The number of patients needed to try to show statistically significant differences, the power for the study, may be drawn from the Phase II studies.

Rehabilitation trials may benefit from more strategically planned, consecutive stages than carried out in FDA-type pharmacological trials [1]. *Stage 1, consideration-of-concept* studies, drawn from animal experiments, theories, and observations, delineates the experimental intervention in a small convenience sample of participants, hence the results must be interpreted with caution. The chosen pre- and post-intervention outcome measures can be tested for their sensitivity to change, along with basic issues such as the safety and best methods to provide the experimental therapy. *Stage 2, development-of-concept* pilots, should optimize the components of the intervention, settle on the most appropriate outcome measures, and examine dose–response effects. A series of these studies or stratification by severity can also identify the characteristics of patients who most need and may best respond to the new intervention. Sample sizes in this stage may be too small to detect the presence or absence of efficacy of a new intervention. *Stage 3, demonstration-of-concept* pilots can build from what has been learned to test at least 15 rather narrowly defined participants in each arm, using random assignment and blinded outcome measures. A control group should receive an active practice intervention aimed at the same primary outcome. A third arm could receive a substantially larger dose of the experimental therapy or a combinational intervention. This stage also assesses the feasibility of a large, multi-site RCT in terms of acquisition and retention of subjects. If only one site performed the trial design, a different investigative group ideally would aim to reproduce positive outcomes based on the optimal dose of the experimental intervention. A well-designed study that reveals no efficacy should be published to counterweight the confirmation bias of positive trials. The raw data for key baseline and outcome measures should also be published, showing a histogram of all changes made by subjects so that the number of responders and non-responders can be visualized. Stage 3 studies, which usually fall within a Phase II design, should suggest at least a medium effect size (i.e., the mean result of the experimental group minus the mean of the control group divided by the standard deviation of the control group is 0.4 or higher). If so,

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as few as 40–60 participants in each arm will be the number required to test optimally for efficacy in a *Stage 4, proof-of-concept*, multi-center RCT. To date, most of the major multi-center RCTs for motor interventions after stroke and spinal cord injury (SCI) have demonstrated the efficacy of an intervention or equivalence between interventions with this number of well-defined subjects, meaning that the number-needed-to-treat will be low, in the range of 4–7 subjects [2–6].

Trials of biological interventions, which to date have been limited to safety trials and uncontrolled (Huang) or less than optimally controlled (Lima) studies, may need some additional modifications to their design. Surrogate outcome measures may be necessary initially to demonstrate short distance axonal regeneration, remyelination, and network modification. Structural and functional imaging and electrophysiology may be necessary to supplement more conventional behavioral measures to reveal subclinical repair. All arms of a biological trial must also receive focused, lengthy rehabilitation for the most clinically likely repair-mediated responses. For example, if the goal is to restore C8 function in patients with American Spinal Injury Association (ASIA) A or B SCI who have C4 to C7 levels, proximal and distal upper extremity strengthening and skilled movements ought to be practiced for at least 12–18 months beyond the biological intervention to ensure that the experimental treatment has had sufficient time to augment rehabilitation.

Types of clinical trials

When clinicians consider the results of research studies for their evidence-based practices, they can classify the level of evidence based, in part, on the design of the trial. Class I studies include prospective, single- and double-blinded clinical trials with randomization to two or more arms. Class II studies include prospective cohort studies, retrospective case-control studies, and clinical series with relevant but not randomized controls. Class III studies may be a clinical series without control subjects or a small series with a single-subject design. The conception for a new treatment can arise from an initial Class II or III study, but regardless of the integrity of the trial design, an intervention does not meet the optimal standard for routine incorporation into practice until a multi-site, Class 1 trial has shown efficacy for clinically important outcomes and, preferably, has been replicated in another group of similar subjects.

Some of the types of descriptive and inferential designs utilized in the rehabilitation literature are listed in Table 1.1. Descriptive studies offer no strength in terms of causal inferences about interventions and outcomes. Quasi-experimental studies lack scientific integrity, because subjects are not randomized, sampling errors are likely, and outcomes are usually not obtained by an impartial observer. Results will be more likely related to chance and the magnitude of an outcome uncertain, compared to data from a successful RCT. Single-subject designs, even multiple N-of-1 studies, may help answer a clinical question about the utility of a drug for a given patient's symptoms or signs in a practice setting, but results are not generalizable. A publishable RCT ought to meet the transparency criteria of the Consolidated Standards of Reporting Trials (CONSORT) statement [7]. The CONSORT checklist appears in Table 1.2. A CONSORT flow diagram is also essential for transparency, revealing how many subjects were assessed for eligibility, reasons for exclusion, and the number randomized to each arm, lost to follow up, and included in the intention-to-treat analysis for the primary outcome measure.

Table 1.1. Examples of clinical research designs (From Dobkin, 2003, courtesy of Oxford University Press [11])

Descriptive
Case study
Cross-sectional survey
Cohort study
One experimental group treat and test
One experimental group treat and test vs. test nonrandomized control group
One experimental group test, treat, retest
Inferential
Quasi-experimental
Multiple treated cohort groups vs. multiple untreated control cohort groups
Experimental group test, treat, test vs. nonrandomized control group test, no treatment, test
Experimental group test, test, treat, test, test, remove treatment or use placebo, test
Experimental group test, test, treat, test, remove treatment or use placebo, test, treat, test
Single-subject designs
N-of-1 randomized, blinded trial
Single time series with repeated baselines
Time series with repeated introduction of intervention
Experimental
Randomized, blinded experimental vs. control group
Randomized, blinded matched pairs
Randomized, blinded block design
Randomized, blinded cross-over design

Randomization

Randomization has three major advantages [7]. First, if properly implemented, it eliminates selection bias by balancing both known and unknown prognostic factors in the assignment of treatments. Without randomization, treatment comparisons may be prejudiced consciously or unintended, by selection of participants of a particular kind to receive a specific treatment. Second, random assignment permits the use of probability theory to express the likelihood that any difference in outcome between intervention groups reflects mere chance. Third, random allocation may facilitate blinding the identity of treatments to the investigators, participants, and evaluators, especially for drug studies, which reduces bias after assignment

Table 1.2. CONSORT checklist of publication criteria for clinical trials (adapted from Moher et al, 2010 [7])

Section/Topic	Checklist item
Title and abstract	Identification as a randomized trial in the title Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)
Introduction	
Background and objectives	Scientific background and explanation of rationale Specific objectives or hypotheses
Methods	
Trial design	Description of trial design (such as parallel, factorial) including allocation ratio Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	Eligibility criteria for participants Settings and locations where the data were collected
Interventions	Interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed Any changes to trial outcomes after the trial commenced, with reasons
Sample size	How sample size was determined When applicable, explanation of any interim analyses and stopping guidelines
Randomization:	
Sequence generation	Method used to generate the random allocation sequence Type of randomization; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how If relevant, description of the similarity of interventions
Statistical methods	Statistical methods used to compare groups for primary and secondary outcomes Methods for additional analyses, such as subgroup analyses and adjusted analyses
Results	
Participant flow (a diagram is strongly recommended)	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome For each group, losses and exclusions after randomization, together with reasons
Recruitment	Dates defining the periods of recruitment and follow-up Why the trial ended or was stopped
Baseline data	A table showing baseline demographic and clinical characteristics for each group and a statistical comparison at baseline
Numbers analyzed	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory
Harms	All important adverse events and harms or unintended effects in each group

Table 1.2. *(cont.)*

Section/Topic	Checklist item
Discussion	
Limitations	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
Generalizability	Generalizability (external validity, applicability) of the trial findings
Interpretation	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information	
Registration	Registration number and name of trial registry
Protocol	Where the full trial protocol can be accessed, if available
Funding	Sources of funding and other support (such as supply of drugs), role of funders

of treatments. The treatment allocation system must also be designed so that the person enrolling participants does not know in advance which treatment the next person will receive. Proper allocation concealment shields knowledge of forthcoming assignments, whereas optimal random sequences prevent correct anticipation of future assignments based on knowledge of past assignments.

Interventions

An intervention ought to hold out the real possibility that it will have a robust effect that is meaningful to patients, if it is to be put through a tedious and expensive RCT. Many trials use subjects with mild to moderate impairment or disability, for which many extant interventions may lead to gains. Few therapeutic strategies, however, are helping those with moderate to severe loss of physical or cognitive functioning [8]. If an intervention at the pilot study stage does not reveal much better than usual results, it may be too incremental to pursue in a multi-center RCT.

Well-defined, experimental rehabilitation therapies should be compared to well-defined control interventions that engage subjects, offer some training (physical or educational), and are relevant to the primary outcome measure. The World Medical Association, which wrote the Declaration of Helsinki for ethical medical research, proposed an amendment in 2008 stating, "a new intervention must be tested against . . . the best current proven intervention." A placebo is acceptable "where no current proven intervention exists." Now that well-designed trials have shown that many motor rehabilitation therapies improve outcomes, if they include a high enough dose of task-related practice and skills learning, investigators involved in neurorehabilitation should drop the notion that no intervention or "usual care" (if that means no specific intervention) is a proper control for an experimental therapy. The control group's assigned activity is an ethical and scientific issue. Participants take on a burden when they participate in research and have personal hopes of improving. Comparing a lot of something to nothing devalues their commitment. The so-called Hawthorne effect suggests that one has to control at least for engagement of the experimental group to account for a placebo effect. Even better, rehabilitation trials should aim for a control intervention that has already been shown to lead to modest gains.

Subjects chosen for trials are often past the time of their post-injury or acute disease, usually at least six months, for example, beyond a stroke, SCI, or exacerbation of multiple sclerosis. To claim that impairment and disability are stable in patients with a chronic set of problems, and that this stability offers a simple solution to "spontaneous gains" that add noise to a trial, may not be correct. Patients may decline over time or adopt compensatory strategies, enough to produce poorer results on testing, yet they retain the latent capacity to improve rapidly if given some training. In addition, a recent medical or psychosocial complication may lessen their abilities transiently. Several solutions can reduce the effects of this confounder to the actual strength of an intervention. Multiple measures could be obtained over one month before or after entry, prior to the start of the interventions, to look for a stable baseline. Perhaps even better, after chronically impaired subjects are screened, one might consider providing a modest intervention to all arms of the trial to make sure that each is at a plateau in the functions that are the focus of the study. Few trials, especially Stage 2 or 3 pilot studies, have taken into account latent capacity that any focused therapy might augment. This strategy may also lessen the possibility of a rapid improvement at the start of the experimental intervention, which can lead to response outliers that affect the integrity of the final analysis.

Primary outcome

The objectives of a trial include the questions that the study is designed to answer, such as efficacy of an intervention to improve walking, but the prespecified hypotheses are the specific questions to be tackled that are amenable to an explicit statistical evaluation, such as testing the null hypothesis. The primary outcome measure for each hypothesis must be stated explicitly, preferably when the trial is initially registered at, for

example, www.clinicaltrials.gov. This measurement is the pre-specified outcome that is of greatest importance to the trialists and their participants. The sample size calculation is usually based on this measure, calculated from pilot studies and other related trials in the literature. More than one outcome can be labeled as primary and secondary, but the statistical analysis should correct for multiple comparisons to lessen the possibility that one of many outcomes will suggest efficacy when it really does not. Pilot studies using a pre- and post-test without a control group, trials with fewer than 20 subjects in each arm, and even large RCTs that pursue data mining for positive results can be misleading when multiple outcomes are measured and tested for statistical significance. The concern to clinicians is that a repeated testing search for confirmational P-values may hide all the negative results that do not appear in a publication. Indeed, for pilot studies with proper controls that are probably underpowered, it may be more useful to set a P-value at 0.1 for one or two primary outcomes than to look at 5–10 outcomes until one gets a *t*-test where P=0.05.

Most rehabilitation trials of a physical intervention will be single-blinded, because the patient will experience the assignment. That does not preclude using sham interventions for trials in which, for example, transcranial magnetic stimulation or surgically implanted cells are the experimental therapy. All subjects would be given the same rehabilitation with their experimental assignment.

Enrichment strategies

Many strategies can improve the promise, feasibility, and economy of an RCT. Investigators must know that they will have access and be able to retain enough subjects for pilot studies and more advanced RCTs. The eligibility criteria, best dose of interventions, and sensitivity of the outcome measures can help reduce the number of subjects that are necessary to power a multi-center RCT. Some of these strategies are listed in Table 1.3.

Table 1.3. Sampling of enrichment strategies for the development of randomized clinical trials

1. Create a clinic-based multi-site system that records key features about potential subjects to identify patients who have the diseases, impairments, and disabilities of interest to investigators. Provide an informed consent at each clinic visit that patients can sign to give permission to be contacted in the future about participation in a trial
2. Consider the reliability and applicability of observations made in prior pilot clinical studies performed on a convenience sample of subjects with a still-evolving experimental methodology. Plan the next stage of studies to address this potential bias
3. Define the essential elements of the intervention and, if possible, their mechanisms of action. Are these robust enough to improve the function of the targeted population?
4. Select the characteristics of the population most likely to respond to a treatment strategy: age, impairments, spared function, comorbidity, optimal time after injury, natural history of change over time, and the impact of lessening an impairment or disability
5. Consider anatomical, physiological, functional neuroimaging, behavioral, genetic, and other potential biomarkers of efficacy to help guide entry criteria for subjects who are most likely to respond
6. Determine the dose (frequency, intensity, and duration) of, for example, task-specific rehabilitation to promote the greatest change in the targeted behavior
7. Use meaningful interventions for control conditions, such as an accepted practice-oriented comparison
8. Perform pre-trial studies that develop realistic estimations of the number of subjects needed to recruit and randomize (anticipated effect size) for a trial
10. Use ratio or interval outcome measures, if feasible, that are sensitive to the spectrum of severity of impairment and disability to be encountered, as well as being sensitive to the likely change induced by the intervention. Use relevant scales of functioning and participation as allied outcomes
11. Minimize the variability of the assessment of outcomes across sites by setting standards that all sites must meet
12. Consider adaptive methods for the treatment phase (dose escalation or incorporate subjects with increasingly greater levels of impairment) and for analysis of outcomes, such as interim measures and Bayesian algorithms

Confounders of clinical trials

The conceptual basis for neurorehabilitation trials increasingly has been found in: (1) preclinical studies in animal models that reveal structural, physiological, or behavioral improvements; (2) theories of motor and cognitive learning paradigms; (3) cortical adaptations or neuroplasticity found in association with training and behavioral gains, imputed from physiological studies such as transcranial magnetic stimulation, functional magnetic resonance imaging, and positron emission tomography. Caution is needed.

Rodent studies may bear little relationship to the type and timing of injury and intervention that is feasible for human subjects. Behavioral measures in mammals are far less sophisticated and telling than in patients. Much of rehabilitation involves cues and feedback that cannot be provided for training of animals. Inbreeding and loss of living in its natural environment alter the responsiveness of animals in ways that are not predictable.

Principles of motor learning to aid training are much discussed, but still remarkably uncertain. For example, task-oriented therapy and greater intensity and duration of practice and feedback are highly promoted, but optimal strategies are still not defined for most interventions and the heterogeneous targets of interventions [8]. Additionally, the context of providing a therapy, such as home versus in a clinic, has not been studied enough to know whether one is better than the other to improve community-based activities. In addition, subjects often undergo one to three hours of formal training from three to six days a week, but investigators have little control or knowledge about what their patients are doing the rest of each day during a trial. Some subjects may be carrying out practice that further drives

gains or inhibits gains, and some may do nothing, which may limit the effects of the formal rehabilitation. This problem can be addressed, at least for mobility-related activities and upper extremity use, by using sensors such as triaxial accelerometers on the limbs of interest to monitor the type and quantity of practice throughout the day (see Volume II, Chapter 6).

Plasticity is becoming an overused, less meaningful basis to justify the deployment of interventions. If a behavior becomes more skilled, learning and alterations in synaptic efficacy are likely. Brain-behavioral relationships related to rehabilitation efforts, however, are difficult to define with certainty. The mere demonstration of a change in a statistical map of regional activation or excitability and the finding of a gain on a test does not imply cause and effect. Thus, plastic adaptations are not yet surrogates for rehabilitation efficacy.

Conclusions

Every stage and phase of clinical trials has limitations in what it can test. The march to an adequately powered RCT has been slow in all of medicine and especially in neurorehabilitation. Pilot studies, however, can make a larger contribution to prepare better for RCTs and explore ways to improve them, if they proceed in a more coordinated set of stages. National and foundation-based programs must also be developed to improve the links across centers with expertise and access to large numbers of potential subjects, to enable collaboration at all stages of development of a novel therapy [9,10], and to maintain expertise in a central clinical and database resource that can move promising treatments into the lives of waiting patients.

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Section 1 Technology of neurorehabilitation: outcome measurement and diagnostic technology

Chapter 2

Understanding the mechanisms underlying recovery after stroke

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Introduction

Approximately 60% of patients with a first stroke will regain their basic activities of daily living (ADL) (19 or 20 points on the Barthel index (BI), or 1 or 2 points on the modified Rankin score) [1]. Eighty percent will regain independence in walking, whereas only 40% to 50% will regain some upper limb function [2,3]. However, a study by European Register of Stroke (EROS) investigators in France, Poland, Italy, U.K., and Lithuania found that, in a population of 2034 first strokes, about 41% (95CI: 39.0–43.7) had a poor outcome, defined as death, institutionalization, or a BI <12 points, at three months post-stroke [4]. Importantly, these variations in outcome were due not only to differences in case-mix variables such as age, gender, stroke severity, stroke subtype, and comorbidity, but also to the location of admission, suggesting that quality of organized stroke care is a critical factor in stroke recovery.

Prospective cohort studies with repeated measurements have demonstrated that almost all stroke survivors will show at least some neurological and functional recovery in the first three to six months [5,6]. The degree of cognitive and motor recovery is independent of vascular territory [7] and is best predicted by the functional status on admission. For example, the largest available prospective study, involving 2213 stroke patients, found the same percentages of gain in terms of the cognitive and motor parts of the Functional Independence Measure (FIM) over a period of ~1 month between admission and discharge, regardless of whether the stroke involved the cerebral hemisphere, brainstem, or cerebellum [7]. This finding is in line with a recent systematic review of prognostic studies, in which the baseline neurological score and initial ADL score at admission were the most important determinants of the final ADL score more than three months after the stroke [1]. Thus, almost all patients show some spontaneous recovery, and the degree of recovery is predicted better by the initial severity of functional deficits (FIM at admission) than by the location of the stroke or the nature of the impairments [7] (see also Volume II, Chapter 46).

The present chapter reviews the mechanisms that underlie the time course of motor and ADL recovery after stroke and discusses the different processes that drive recovery of activities (i.e., functional recovery). The chapter uses the definition of activities of the International Classification of Function, Disability, and Health (ICF) model (WHO, 2010) [8]. This model provides a framework for classifying the effects of stroke rehabilitation on individuals (Figure 2.1) in terms of pathology (disease or diagnosis), body functions (i.e., impairments), limitations in activities (i.e., disability), and restrictions of participation (i.e., handicap) [6]. In this regard, we distinguish between "outcome" and "recovery." Outcome reflects the patient's ability to execute a particular function or task at a defined moment after a stroke, whereas recovery refers to the process of functional improvement over time. The next section further explains the term recovery in relation to the ICF. Finally, a neurobiological model for understanding skills acquisition is presented, emphasizing the importance of translational research to improve our knowledge about *what* and *how* patients learn when they show functional recovery after stroke [9].

What do we mean by recovery after stroke?

Recovery of body functions and activities most likely involves concurrent spontaneous and learning-dependent processes, including restitution (restoring the functionality of damaged neural tissue), substitution (reorganization of partly spared neural pathways to relearn lost functions), and compensation (improvement in the disparity between a patient's impaired skills and the demands imposed by his/her environment [5,6]. Recovery after stroke can be defined at the impairment level, such as improvement of the strength of and sensation in the paretic limb. In this case, recovery reflects the return of body functions performed by the same end effectors (i.e., the same body part, such as a specific muscle, that interacts with an object or the environment) [10]. As a consequence, the skill or ability to execute a meaningful task is restored with the same quality of motor control as before the stroke [10].

Functional recovery may also reflect improvement as a result of adaptation or compensation strategies, in which the patient learns to deal with existing underlying neurological

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Table 2.1. Terminology

	Body structure (i.e., the brain)	Body function (i.e., upper limb)	Activity (a person)
Recovery	Any change in the structure that leads to improved function *(Includes restitution and substitution)*	Improvement of the ability to perform a movement *(Includes compensation and restitution)*	Improvement of the ability to perform a functional task *(Includes compensation and restitution)*
Restitution	Repair: changes toward the original state	Identical employment of body components* as before the injury	Identical task performance as before the injury
Compensation/ substitution	Alternative employment of body structures	Alternative employment of the same body components as before injury*	Task performance using alternative limbs and/or environmental adaptations

Note: A classification of recovery, compensation/substitution and restitution, based on the ICF model. A stroke can cause changes in various body structures (e.g., the spinal cord, the brain, and/or muscles). A change in a particular body structure can influence a body function (e.g., muscle power, muscle tone, or the coordination of voluntary movements), and a change in a body function can influence the performance of an activity (e.g., eating, dressing). We suggest that recovery can be the result of both compensation/substitution and restitution within the defined levels of the ICF classification.
* A body component is defined as a collection of body structures that contribute to a specific body function.

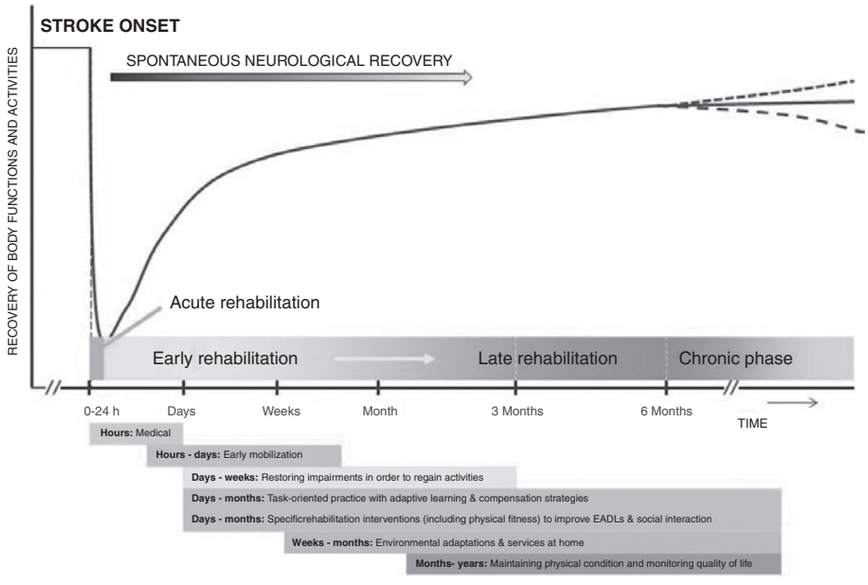

Figure 2.1. Hypothetical illustration of the nonlinear pattern of stroke recovery in a sample with a first-ever, ischemic middle cerebral artery stroke. Adapted from Langhorne et al., 2011 [6]. (For color image, see color plate section.)

impairments (Table 2.1). Here, motor adaptation can be defined as the appearance of new motor patterns resulting from the use of motor elements that have remained intact, at the body function level. Motor compensation can be defined as accomplishing functions by using different end effectors. For example, most patients with mild-to-moderate hemiparesis develop trunk movements to compensate for limb weakness. If the compensatory movements are counterproductive, they can be reduced by appropriate interventions, such as trunk restraint for arm reaching tasks [11,12]. Without looking at the quality of task performance, it is impossible to distinguish recovery as a result of neurological repair from adaptive compensation, when they use the same end effectors [10]. The ultimate form of compensation is that achieved by using different end effectors, in which case the task is taken over or completely substituted. This form of compensation (or replacement) is called "substitutive compensation" [10]. For example, patients may learn to use the non-paretic limb to perform a grooming task or brush their teeth. Many studies have shown that improvements in activities like gait [13] and reaching [11] are largely dependent on adaptations by using end effectors in a different way than before the stroke or than healthy subjects do.

It is important for clinicians and scientists to distinguish between functional recovery as a result of neurological repair and recovery resulting from compensation strategies [10]. Indeed, there has been a long-standing debate in rehabilitation medicine as to whether specialists should strive for restitution of body functions or allow patients to learn adaptation strategies. It seems reasonable to suggest that compensatory or substitutive movements may be encouraged in patients with severe impairment and a poor prognosis after the first weeks post-stroke, in order to maximize their abilities at the activities' level, whereas the aim in patients with a more favorable prognosis may be to repair neurological functions. For example, strategies

to increase walking speed involve encouraging relatively larger arm and leg swing amplitudes on the nonparetic than on the paretic side [14]. In the upper limb, motor compensations may involve the use of movement patterns that incorporate trunk displacement and rotation, scapular elevation, and shoulder abduction and internal rotation [11,15]. Examples of adaptive compensatory strategies include the use of increased trunk movement to assist arm and hand transport and to facilitate hand positioning/orientation for grasping [10]. During the first six months post-stroke, both learning processes–restitution and substitution–are complementary to each other. The balance between the strategies depends on the amount of energy, speed, and accuracy that is required to perform a particular task.

The distinction between restitution (or repair) and substitution (or compensation) has important implications for stroke rehabilitation [10,16]. During the first three to four weeks post-stroke, the brain shows a heightened level of homeostatic neuroplasticity, due to an upregulation of growth promoting genes [17]. Thus it seems reasonable, although still unproven, that in the early stages after stroke, therapists should focus on supplementing spontaneous biological recovery with restoration of neurological functions, whereas in later stages, rehabilitation should focus on learning adaptation strategies.

How do we define spontaneous biological recovery after stroke?

At the level of body function, spontaneous biological recovery may be defined as the amount of neurological improvement of body functions such as synergy, attention, and strength that is determined by the passage of time alone [9]. Most neurological improvement is found within the first days and weeks after stroke. As a result of these early nonlinear changes in body functions, patients also show a nonlinear recovery pattern at the level of activities. For example, longitudinal regression analysis of change scores shows that, after correction for age, gender, hemisphere, type of stroke, and type of intervention, the passage of time can explain 40% (or 8 points) of the observed improvement in BI, which ranges from 0 to 20 points [1,5]. Thus, the final BI at six months can be predicted by adding about 8 points to the initial BI measured at the end of the first week after stroke [18]. The processes responsible for this spontaneous biological recovery are unknown, but they seem to be largely independent of age [5,19,20] in a first stroke. This suggests that there is no justification for denying rehabilitation to patients solely on the basis of advanced age [19]. More importantly, these findings suggest that the main cause of poorer ADL outcomes in the elderly is probably reduced levels of independence caused by pre-stroke comorbidity [1,21].

Longitudinal studies with repeated measurements show that the early time-dependent functional changes are limited to the first four to 10 weeks post-stroke [5]. This is in agreement with the findings of a number of prospective cohort studies, highlighting the nonlinear pattern of recovery after a stroke [22–26]. For example, recovery of motor function (assessed with the Fugl–Meyer motor score) and ADL (assessed with BI) was found to level off between four and 12 months after stroke [5,27,28]. The nonlinear time-dependent changes in neurological functions that occur after stroke, regardless of the type of services delivered, have not been analyzed extensively [5,29] and are still poorly understood. As a consequence, the literature lacks a uniform definition of spontaneous biological recovery. Nevertheless, this nonlinear recovery may be conceptualized as a non-learning-dependent mechanism that is active mainly in the first weeks after stroke.

Are we able to modulate the pattern of functional recovery?

There is no doubt that the use of tissue plasminogen activator (tPA or thrombolysis) is the most effective therapy when applied within a three-hour time window in patients with an acute ischemic stroke. However, fewer than 10% of the stroke patients fulfill the criteria for recombinant tPA (rTPA). For the others, we must develop treatments designed specifically to reduce neurological deficits, by designing appropriate rehabilitation services. The main aim of rehabilitation is to restore activities according to the terms of the ICF model so that a satisfactory quality of life can be achieved [30]. Up to 2011, more than 600 randomized controlled trials (RCTs) on effects of exercise therapy had been published in scientific, peer-reviewed journals. There is strong evidence that repetitive task-oriented training improves gait speed, walking distance, walking ability, transfers, and ADL [16,31–33]. Current findings suggest that higher training intensities speed up functional recovery after stroke, whereas adding activities produces a greater degree of recovery [5,33–35]. However, very little is known about the dose–response relationship between the amount of exercise and functional improvement, because of the lack of appropriate experimental designs and dose–response trials. This problem needs to be solved in the near future. To date, a cumulative meta-analysis combining 20 RCTs involving 2686 subjects suggests that more intensive therapy results in significantly greater improvements in ADLs (SES [fixed]: 0.13 standard deviation units [SDUs]; CI: 0.06–0.23; $Z=3.252$, $P<0.001$) [34]. This SES (summary effect size) indicates an overall change of about 5% as a result of more intensive therapy, which corresponds to a 1-point change on the 20-point BI scale. However, large differences were found among RCTs with respect to the total amount of additional therapy provided, as well as in the timing and focus of the interventions applied. Some trials concentrated on gait training alone, others on dexterity, and some restricted their efforts to facilitating ADLs in general. These findings are in line with several other systematic reviews that suggested that repetitive task training has a meaningful impact on daily living function [36]. However, this evidence was based mainly on studies of augmented exercise training for the lower limb and for patients who started their trial within the first six months post-stroke [34,36].

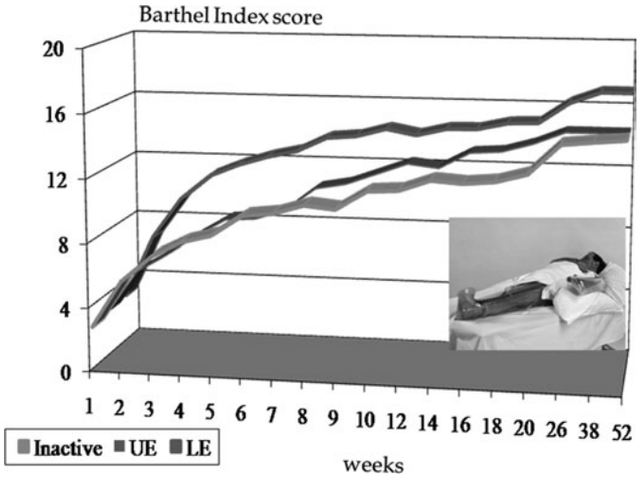

Figure 2.2. Mean recovery patterns on the Barthel index (n=101) in patients immobilized by an air splint (gray curve) or engaging in an active motor training program focusing on lower limb function (black curve). No statistically significant differences were found at six months post-stroke, suggesting faster recovery for those who received more intensive rehabilitation in the first 20 weeks. Inserted photo depicts a patient with an airsplint. Adapted from Kwakkel et al., 1999 [33]. (For color image, see color plate section.)

In addition to the evidence for a critical effect of intensity of practice, almost all well-conducted trials suggest that the effects of exercise training are context- and task-specific; that is, the effects of any treatment are restricted mainly to those tasks that are directly trained in therapy. The evidence for context and task specificity suggests that training should be applied functionally and preferably in a context that is meaningful to the patient. Both elements–augmentation and task specificity of treatment–were integrated in a randomized controlled study involving 101 patients with a primary middle cerebral artery (MCA) stroke [33]. All patients were assigned to one of three intervention groups and assessed 18 times in the first year after stroke. Subjects who received 30 minutes of additional training each working day for 20 weeks showed faster improvements in gait (lower limb rehabilitation group) and dexterity (upper limb rehabilitation group) than control groups who were treated with airsplint immobilization of the lower and upper paretic limbs, respectively (Figure 2.2). However, the effects were only significant up to 20 weeks post-stroke, suggesting that active task-specific training may merely accelerate functional recovery. The long-term effects remain unclear. A follow-up study showed that, on average, patients maintained the same level of activity for up to one year after stroke. Although many patients (10%–30%) showed, from six months onward, further significant improvement or deterioration in functional outcomes such as gait speed, dexterity, or ADL [37], it was not possible to predict which patients would change. However, beyond six months post-stroke, patients with incomplete functional recovery of the upper or lower limb were most likely to change significantly, probably due to learned non-use [37].

This longitudinal study highlighted three important issues. First, the effects of rehabilitation are largely temporary and are greatest in the first six months after stroke. Second, the effects are relatively small compared to the substantial functional recovery that often occurs (about 10% of the variance in the outcome) and are largely independent of the type of therapy that is applied. Third, the improvement in disabilities, including those affecting gait and dexterity, which are nonlinearly related to underlying impairments like strength and synergy, need not involve reversal of underlying impairments; they can be partly explained by the use of behavioral adaptation strategies [16].

In line with the evidence for the importance of intensity and task specificity in exercise training, task-oriented fitness training (e.g., using workstations in a circuit) has been shown to improve gait speed, walking distance, and gait-related ADL [38–40]. Speed-dependent treadmill training improves gait speed and walking distance, whereas electromechanically assisted gait training significantly increases the probability of regaining independent gait (and walking distance) [41]. Occupational therapy (OT) service at home improves extended ADL, including outdoor mobility [42,43] and basic ADL [44], and prevents deterioration after stroke [42]. Finally, constraint-induced movement therapy (CIMT) improves upper limb function [45–47]. These systematic reviews suggest that the intensity and the task and context specificity of training are the main drivers of functional improvement, and that the trained task should be relevant to the patient.

Several interesting treatment approaches to improve functional recovery have been proposed, however sufficient rigorously controlled studies to prove their efficacy are lacking. These include (1) external auditory rhythms during gait to improve stride length and walking velocity [48]; (2) bilateral arm training supported by auditory rhythmic cueing to improve upper limb function [49]; (3) robot-assisted training of the paretic upper limb to improve upper limb motor function ([50]; (4) mirror therapy to improve upper limb function [51]; (5) (non-task-oriented) cardiorespiratory fitness training, including cycling exercises, to improve walking distance [39]; and (6) strategy training for extended ADLs in patients suffering from dyspraxia after stroke [52].

For several other proposed approaches, evidence is either contradictory or completely lacking. These include (1) programs focusing on muscle strength training of the lower limb alone [39]; (2) visual feedback therapy while standing [53]; bio- and EMG-feedback training for upper or lower limbs [54]; (3) treadmill training with and without body weight support to improve walking [55]; (4) limb loading, or using garments for gait training [56]; (5) acupuncture [57]; and (6) amphetamines combined with exercise therapy [58,59]. Finally, there is no evidence to support specifically neurological treatment approaches [6], including Bobath therapy [60], after stroke.

In any case, the impact of early rehabilitation relative to spontaneous recovery is small. In well-conducted randomized clinical trials, rehabilitation accounted for 5% [34] to 10% of