



SPECIAL ARTICLE

# Designing studies and reviews to produce informative, trustworthy evidence about complex interventions in rehabilitation: a narrative review and commentary

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## ABSTRACT

According to Cochrane Rehabilitation’s recently published definition for research purposes, rehabilitation is inherently complex. Rehabilitation teams frequently implement multiple strategies concurrently, draw on input from a range of different health professionals, target multiple outcomes, and personalize therapeutic plans. The success of rehabilitation lies not only in the specific therapies employed, but also in how they are delivered, when they are delivered, and the capability and willingness of patients to engage in them. In 2021, the UK Medical Research Council (MRC) and the National Institute of Health Research (NIHR) released the second major update of its framework for developing and evaluating complex interventions. This framework has direct relevance to the development and implementation of evidence-based practice in the field of rehabilitation. While previous iterations of this framework positioned complex interventions as anything that involved multiple components, multiple people, multiple settings, multiple targets of effect, and behavior change, this latest framework expanded on this concept of complexity to also include the characteristics and influence of the context in which interventions occur. The revised MRC-NIHR framework presents complex intervention research as comprising the following four inter-related and overlapping phases: 1) development or identification of the intervention; 2) feasibility; 3) evaluation; and 4) implementation, with different methods and tools required to address each of these phases. This paper provides an overview of the MRC-NIHR framework and its application to rehabilitation, with examples from past research. Rehabilitation researchers are encouraged to learn about the MRC-NIHR framework and its application. Funders of rehabilitation research are also encouraged to place greater emphasis on supporting studies that involve the right design to address key uncertainties in rehabilitation clinical practice. This will require investment into a broader range of types of research than simply individual-level randomized controlled trials. Rehabilitation research can both learn from and contribute to future iterations of the MRC-NIHR framework as it is an excellent environment for exploring complexity in clinical practice.

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Rehabilitation is inherently complex. Cochrane Rehabilitation’s recent work, drawing on the knowledge and experience of multiple international experts and community partners to develop a definition of rehabilitation

for research purposes, perfectly illustrates this complexity.<sup>1</sup> Rehabilitation teams frequently implement several strategies concurrently, involve coordinated input from a range of health professionals, target multiple outcomes, and personalize therapeutic plans. The success of rehabilitation programs often lies not only in what specific therapies (single interventions) are employed, but also in how they are delivered by health professionals, when they are delivered, and the capability and willingness of patients to engage in them.

From this perspective, being a rehabilitation professional is a bit like being a pâtissier (pastry chef). As undergraduates, health professionals learn about the “ingredients” of rehabilitation (exercise, functional training, psychological therapies, adaptive technologies, targeted pharmaceuticals and so forth) — like the ingredients of a cake. However, it is not until new graduate health professionals have gained some years of experience — and until some consideration is given to each patient’s individual goals, resources, strengths, and preferences — that they learn the best combinations of these ingredients, the correct order to add them, how much attention or “optional extras” are needed and when, in order to adjust the shape, texture, and flavor of rehabilitation to create something that best meets the needs of the individual recipient.

This is not to say that long-term professional experience alone should guide clinical decision making (there is, after all, extensive literature on the risk of cognitive bias and personality traits impacting on safe and effective healthcare decision making).<sup>2</sup> Rather, the purpose of this analogy is to illustrate the complexity of rehabilitation as a discipline, and how evidence-based interventions from single randomized controlled trials (RCTs) or even systematic reviews of these RCTs, cannot be successfully implemented without sound clinical judgement.<sup>3</sup>

In other words, knowledge about what “ingredients” of rehabilitation should be delivered and how they are offered are central to the effectiveness of rehabilitation. Further to this, rehabilitation programs are offered to people with agency (*i.e.*, patients with control over their own personal decisions and actions), situated within a series of complex environments (*i.e.*, clinics, hospitals, families, and communities), within systems at therapeutic dyad, interprofessional team, healthcare organization, and broader socio-economic levels. Understanding complexity is, therefore, central to understanding rehabilitation.

In 2021, the UK Medical Research Council (MRC) and the National Institute of Health Research (NIHR) released the second major update of its framework for developing

and evaluating complex interventions.<sup>4, 5</sup> Originally published in 2000,<sup>6, 7</sup> and previously updated in 2008,<sup>8</sup> the MRC-NIHR framework has evolved from being an addendum to methods for RCTs into an explicit challenge of the hegemony of efficacy and effectiveness trials in health science research. The new framework positions research into efficacy and effectiveness as valuable but equal to — not better than — research that explores questions from a theory-based or systems perspective. This framework calls for much greater emphasis on, and investment into, a more comprehensive range of study designs than just RCTs — to include qualitative and mixed methods studies, non-randomized designs, n-of-1 trials, hybrid effectiveness-implementation designs, and so on. Indeed, one published response to the revised framework referred to the “hierarchy of evidence” as being “consigned to history.”<sup>9</sup>

Behind this criticism of past perspectives on the hierarchy of evidence is a desire to generate better information to guide decision-making in the “real world” of clinical practice and healthcare policy. The concept of a “real world” clinical setting is used throughout this paper as a convenient phrase to draw a distinction between clinical practice that occurs in everyday, non-simulated, non-manipulated environments and clinical practice that occurs within the carefully controlled or managed contexts of research studies, which are arguable more “artificial” in several regards (*e.g.*, dedicated funding, limits on who can participate and what can be provided, restrictions on clinical decision making, greater control over management and monitoring of service delivery etc.). RCTs are an excellent tool — arguably the best tool — for providing evidence of a causal link between a single intervention (*e.g.*, an exercise, a drug, a psychological technique) and improvements in a particular health domain (*e.g.*, cardiovascular fitness, blood pressure, anxiety) within carefully controlled conditions. However, in isolation, RCTs provide little information about what influences patient adherence to an intervention, how an intervention achieves its effects, how people feel about an intervention, why it is effective for some but not others, and how the intervention performs within the broader context of a healthcare system. RCTs are also arguably better suited to address questions regarding the effectiveness of biological interventions rather than behavioral or environmental interventions.<sup>10</sup> For example, a recent pragmatic benchmark study found that a personalized management approach to rehabilitation of idiopathic scoliosis, which accommodated each individual patient’s presentation, behavior and circumstance in real world clinical practice, was 40% to 70% more effective at limiting

spinal curvature when compared to highly standardized “per protocol” treatment approaches used in benchmarked RCTs.<sup>11</sup>

Furthermore, RCTs may exclude large swaths of everyday clinical populations (frequently older adults and people with comorbidities,<sup>12</sup> women,<sup>13</sup> and minority groups)<sup>14</sup> — sometimes by neglect but other times by design, *e.g.* to control for variables that may confound evidence of a treatment effect. For example, one population-based respiratory health survey found that only 4% of people with asthma met the eligibility criteria for RCTs used in developing the Global Initiative for Asthma Guidelines,<sup>15</sup> greatly reducing confidence in their generalizability. For these reasons, authors of the MRC-NIHR framework for complex interventions state that, in addition to effectiveness trials, an evidence-informed healthcare sector needs more investment in research that provides information about “whether and how [an] intervention will be acceptable, implementable, cost effective, scalable, and transferable across contexts.”<sup>14</sup>

The purpose of this paper is to review the MRC-NIHR’s latest framework for developing and evaluating complex interventions from the perspective of rehabilitation. The paper provides an overview of this framework, examples of the application of its core ideas in rehabilitation research, and a discussion of what the rehabilitation research community needs to consider to better align with this framework in the future.

### What are complex interventions?

There is no operational definition that can easily separate “simple” from “complex” interventions, and what makes an intervention “complex” has been considerably debated. Indeed, Petticrew argued that “in fact there are no ‘simple’ or ‘complex’ interventions”<sup>16</sup> because all interventions, including pharmaceutical ones, are complex. They have only been made simple by pragmatic and reductive research practices, which strip interventions down into single components and which involve extensive strategies to control for bias and variation in populations, behaviors, clinical context, and practices when conducting clinical trials.

One important distinction is that “complex” in this context should not be misunderstood to mean “complicated.” Some relatively simple interventions can be complicated to understand or in their mechanism for effect. For example, botulinum toxin to treat spasticity is reasonably simple to deliver in that it can be a single intervention and does not require a multidisciplinary approach or even pa-

tient engagement to have an effect. However, how botulinum toxin achieves its effect on muscle spasticity and how and why this effect diminishes over time is complicated. In other words, the complexity of an intervention refers to the context in which it is delivered, not how difficult it is to understand.

That said, even in the context of research, the complexity of an intervention is usually considered to lie on a continuum from less to more complex. In the original MRC guidelines, complex interventions were described as those that involved multiple components — the more components to an intervention, the more complex it was.<sup>6</sup> Examples of complex interventions from this perspective included stroke units, group psychotherapies, and cognitive behavioral therapy for depression.

In the first update of the MRC-NIHR guidelines, characteristics that made an intervention complex were extended to include the number and variability of outcomes targeted, the degree of flexibility and individualization permitted in the delivery of an intervention, and the number and difficulty of behaviors required of people delivering or receiving the intervention.<sup>8</sup> For instance, interventions that required certain actions or behaviors from the people delivering the intervention (*e.g.* particular expertise, skills, personality, or communication style) or from the people receiving the intervention (*e.g.* their ability, willingness, or effort when engaging in therapeutic activities) were considered more complex. In this context, the content of single, highly standardized therapies (*e.g.* a per-protocol incremental exercise program) would be considered “simple” whereas the full rehabilitation process (*e.g.* incorporating individualized goal selection; choice and variation in type, intensity and duration of exercises; psychological approaches to increase patient engagements and adherence etc.) would be considered “complex.” However, “complexity” was still viewed primarily as a characteristic of the intervention itself.

In the latest MRC-NIHR framework, the complexity of an intervention is described as arising from both the *characteristics* of the intervention and from the *interaction* between the intervention and the study or clinical context.<sup>5</sup> An intervention is still more complex if it involves multiple components, multiple people, multiple settings, multiple targets of effect, and behavior change. However, interventions are also considered increasingly complex when contextual factors influence how and to what degree outcomes, including unexpected negative effects, are generated. For this reason, the MRC-NIHR’s framework conceptualizes complex interventions as “events in systems,”<sup>14</sup>

TABLE I.—Examples of properties of complex adaptive systems from rehabilitation research.

System property	Example from rehabilitation
Emergence	• Information in a participant consent form encourages people in a “control” group to seek alternative treatment they would have not otherwise considered.
Feedback	• Positive experiences of early mobilization influences patients’ motivation to engage more assiduously in other therapeutic activities after stroke.
Adaptation	• Engagement with other people in a spinal cord injury rehabilitation unit encourages newly disabled young adults to think more ambitiously about work, independent living and trying new things.
Self-organization	• A pulmonary rehabilitation class self-organizes a social group that continues to meet after the program finishes.

with these systems being characterized by properties (e.g. emergence, feedback, adaptation, self-organization) that make them dynamic and adaptive. Examples of some of these properties in the context of rehabilitation research are presented in Table I.

Similarly, the complexity of rehabilitation has been discussed and debated for some time. Tools such as the International Classification of Functioning, Disability, and Health (ICF),<sup>17</sup> the Rehabilitation Treatment Specification System,<sup>18</sup> and the International Classification of Service Organization in Rehabilitation,<sup>19</sup> have been developed in order to unpack and better understand some of this complexity. Building on the concepts underpinning the ICF, Cochrane Rehabilitation’s recent definition of rehabilitation for research purposes posited that rehabilitation is a multimodal, person-centered (*i.e.* individualized) process (*i.e.* changing in time), which requires collaboration between the people providing and the person receiving or engaging in it.<sup>1</sup> This definition also highlights the importance of considering context when evaluating rehabilitation.<sup>1</sup> The inherent complexity of rehabilitation typically requires holistic management, often addressing multiple factors simultaneously. Within the ICF framework, this complexity results from the many variables that ultimately determine the capacity a person might have for activity and participation. Contextual factors (across a range of temporal, environmental, and social domains) can influence the degree to which people might participate in a rehabilitation program. Equally, contextual factors may even be the target of interventions (e.g. changing the physical or social environment to optimize the functioning of a person with a disability or chronic health condition).<sup>1</sup> Consideration of guidelines for research into complex interventions is therefore directly relevant to the task of developing a scientific evidence base for rehabilitation.

### Designing studies of complex interventions

By their very nature, RCTs and systematic reviews of RCTs simplify the complexity of everyday clinical prac-

tice for the purpose of evaluation.<sup>16</sup> Complex interventions are challenging to study precisely because of the untidiness of human behaviors and interaction in real world settings. Research into complex interventions needs to be designed to explore and account for variability in how an intervention is delivered by a health professional and responded to by a study participant; how the components of an intervention interact with each other or with aspects of the participant’s presentation; and in the range of outcomes that are relevant or meaningful to individual people. From this perspective, complexity-informed research “attends to complexity rather than focusing on controlling for it.”<sup>5</sup> Of note, research into these aspects of complex interventions cannot be addressed by a single, gold-standard study design, but instead requires a construction of information and evidence across a range of study types over time.

The revised MRC-NIHR framework presents complex intervention research as being comprised of four inter-related and overlapped phases: 1) development or identification of the intervention; 2) feasibility; 3) evaluation; and 4) implementation.<sup>4</sup> Each of these phases are connected by a common set of six core elements: 1) consider context; 2) develop, refine, and (re)test program theory; 3) engage community partners (the phrase in the MRC-NIHR guidelines is in fact: “Engage Stakeholders”. However, we are aware that the colonial roots of the term “stakeholders” has been contested, so intentionally refer to “community partners” instead);<sup>20</sup> 4) identify key uncertainties; 5) refine interventions; and 6) economic considerations.<sup>4</sup> The MRC-NIHR advises against approaching these phases sequentially, and instead suggests that researchers begin by identifying “key uncertainties about the intervention in question,”<sup>4</sup> and to repeat the phases as needed.

Development and identification of an intervention involves using inductive or abductive reasoning from clinical experience, from new or existing research evidence, or from theory to design a new type of intervention or fully describe an already existing one. In this context, theory is useful for developing ideas (often hypotheses) about the active ingredients of an intervention, how they should be

combined, and why they are expected to work. The exercise consists of tentatively linking specific active ingredients to specific clinical goals within a plausible relationship, which would, on the one hand, facilitate the selection of appropriate outcome measures and, on the other hand, help generate hypotheses to be tested. In order to facilitate communication and coherence across a field of practice, such as rehabilitation, active ingredients should be defined following standardized and agreed nomenclature.<sup>18</sup>

Feasibility studies involve methods to explore whether it is practical to implement an intervention (*e.g.*, its acceptability, “fit” with current clinical practices, training requirements for health professionals, adherence by participants, cost, etc.) or possible to evaluate it (*e.g.*, addressing uncertainties such as likely recruitment rates, data collection, required samples sizes for a full powered study etc.). This information is often needed to ensure that a future evaluation of an intervention is possible and likely to produce information that will meaningfully inform practice.

Evaluation studies focus on assessing whether an intervention works (*e.g.*, its efficacy). However, under the new MRC-NIHR framework, evaluation studies may also generate a better understanding of how an intervention might work, how it interacts with contextual factors, and how evidence can be used to support changes in clinical practice. RCTs and variants of RCTs (*e.g.* cluster-RCTs) have an important role to play in this part of the process of development and evaluation of complex interventions.

Implementation research is designed to inform decisions about the application of complex interventions in real world settings. This research involves methods to explore ways to increase the impact of an intervention, improve and update it, and to better target its effects. Implementation research is about understanding what is needed to transfer any gains identified in a carefully controlled experimental setting, to the messiness and ambiguity of real-world practice. This includes for example consideration of the broad context of individual patients’ lives, needs and preferences and responses to treatment; the impact of co-morbidities of intervention delivery or outcomes; and financial and organizational constraints on upscaling or delivering an intervention.

A key point in the most recent MRC-NIHR framework is that no single study design can achieve all these objectives across the different phases of developing and evaluating clinical interventions. Research into unbiased estimates of intervention effectiveness is useful but limited in the scope of what information can be provided. Instead of relying solely on meta-analyses of collections of RCTs,

networks of diverse evidence drawing on a wide range of methods are needed. However, in comparison to the well-established methods of RCTs, alternative methods for better understanding complex interventions and their application are still largely in their infancy. Purposeful efforts to fund and explore the use of other ways of developing information to guide clinical practice are needed. In other words, funders of healthcare research need to place greater emphasis on the degree to which a study is the right design to address “key uncertainties” in clinical practice – to draw on the language of the MRC-NIHR framework – while researchers need to put more explicit effort into identifying and documenting these key uncertainties, and into justifying the best ways of addressing them.

Supplementary Digital Material 1 (Supplementary Table 1) provides an overview of the strengths and weaknesses of a range of common research methods that are potentially useful in each phase of complex intervention development and evaluation. This table has been developed beginning with information from a systematic review of methods for evaluating complex interventions published by Minary *et al.*,<sup>21</sup> which we have adapted and expanded to better align with all phases of complex intervention research proposed by the MRC-NIHR framework.<sup>4</sup>

### Examples of research on complex interventions in rehabilitation

As noted in the introduction to this paper, while simple interventions are possible in rehabilitation (interventions for rehabilitation), rehabilitation programs are complex — by definition. In this section, two interventions — one from the field of vocational/occupational rehabilitation; the other from neurorehabilitation — are used to illustrate how research has already applied different strategies to explore complexity in the context of rehabilitation.

Of note, while the MRC-NIHR guidelines have been highly influential and influenced by the development of health science research methods over the past twenty years, few rehabilitation researchers have cited this framework in their journal publications. For example, a forward citation search in Medline of the top 30 rehabilitation journals by Journal Impact Factor (Web of Science) for all articles that have referenced any of the seminal publications on the MRC-NIHR guidelines<sup>4, 5</sup> or its predecessors<sup>6, 8</sup> identified only 65 such articles after removal of duplicates. (Supplementary Digital Material 2: Supplementary Text File 1). The majority of these 65 articles were commentaries on methodology themselves or only referenced the

MRC framework in passing (*i.e.* did not provide an in-depth discussion of how the researchers had applied the framework to the development of their research methods). As such, we have selected these two examples below not because they have been published with explicit reference to the MRC-NIHR guidelines, but because they usefully illustrate how a range of the concepts in these guidelines can be applied to rehabilitation research.

### Research on reducing work disability

One complex rehabilitation program that has been rigorously evaluated is integrated care for chronic low back pain causing work disability, also known as the Sherbrooke Model.<sup>22</sup> Chronic low back pain is among the most common, disabling, and burdensome conditions globally.<sup>23, 24</sup> Few effective treatments or solutions are available, and disability due to low back pain is affected by complex interactions of personal, clinical, psychological, contextual (*i.e.*, physical and social work environment), and systems-level factors.

Integrated care involves reducing disability due to low back pain through education and graded activity aimed at increasing patients' functional ability, as well as workplace interventions to reduce work demands and associated contextual barriers. This complex intervention has been informed by the Arena of Work Disability, which conceptualizes work disability as being influenced by multiple systems (*i.e.*, personal, workplace, healthcare, and legislative/insurance systems).<sup>25</sup> The Arena highlights factors that put people at risk of developing disability due to musculoskeletal pain and postulates avenues for intervention. Integrated care is delivered through the health care system to improve personal and workplace systems and reduce work disability.

Integrated care for reducing work disability due to low back pain has been evaluated in Canada and the Netherlands, with the Dutch study being an excellent model of a complex intervention evaluation. Development of the Dutch intervention and evaluation was informed by theory<sup>25</sup> and an intervention mapping approach,<sup>26</sup> a proposal was published and registered,<sup>27</sup> and a multi-pronged evaluation of the intervention undertaken. This included a process evaluation to assess feasibility of the intervention and the evaluation design using surveys and chart reviews.<sup>28</sup> This research established that the program was promising in terms of feasibility, satisfaction, and compliance of the participants, their work supervisors and health care professionals.

A subsequent RCT of integrated care for chronic low back pain, with a 12 month-follow up, found that participants receiving integrated care were more likely to sustainably return to work within the following year.<sup>29</sup> They also experienced lower self-reported disability, but with no corresponding improvement in pain. Lastly, an economic evaluation was conducted alongside the trial to determine impact.<sup>30</sup> This used cost-effectiveness planes and acceptability curves to demonstrate that integrated care was cost-effective compared to usual care (every £ 1 invested in integrated care returned an estimated £ 26).

This intervention's development and thorough evaluation included several of the six core elements recommended in the new framework for developing and evaluating complex interventions.<sup>4</sup> Consideration was given to how the intervention interacted with its healthcare and workplace contexts. The evaluation had an underpinning program theory,<sup>26</sup> and diverse perspectives were considered and included. Key uncertainties were explored and the intervention, developed initially in Quebec, Canada, was refined for the Dutch context. Lastly, comparative resource and outcome consequences of the intervention were considered. An overview of how this research fits within the MRC-NIHR framework for developing and evaluating complex interventions is presented in Figure 1.

### Research on taking charge after stroke

“Take Charge” is a community-based, psychological intervention designed to help people take control of their own recovery after stroke. It is described by its developers as a conversation between a person with stroke, their family, and a facilitator — using an illustrated booklet to stimulate ideas about goals and self-management behaviors. This “talk therapy” is delivered as one or two brief 40- to 60-minute conversations in a person's home soon after discharge, with the aim of improving self-efficacy, independence, and quality of life. Of particular note, the trained facilitator of this intervention is intentionally not a health professional in order, in part, to de-medicalize the recovery journey. The intention of this intervention is that the person with stroke, with input from their family, does all the talking and writing, leading the work rather than the health professional. The Take Charge intervention is an excellent example of how a deceptively simple-looking intervention can be complex.

The Take Charge intervention was initially developed to address inequity in stroke outcomes for Māori and Pacific people in New Zealand.<sup>31</sup> It was developed on the basis

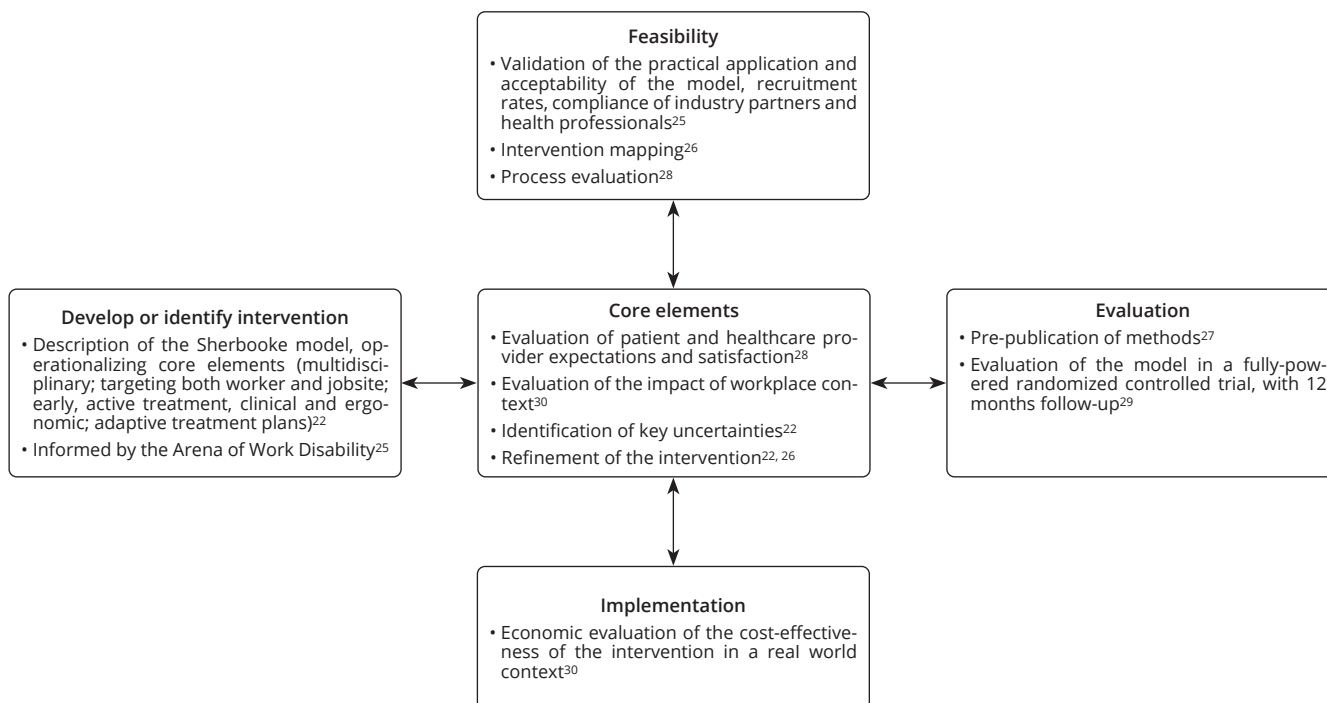


Figure 1.—Mapping research on integrated care for chronic low back pain causing work disability against the MRC-NIHR framework for developing and evaluating complex interventions.

of earlier qualitative research that had identified the value placed on being able to “take charge” of one’s own recovery by people with chronic health conditions,<sup>32</sup> and on Bandura’s theory of self-efficacy and its potential application to rehabilitation.<sup>33</sup> The preliminary study of the Take Charge intervention was in fact investigated alongside a second possible approach to improve self-efficacy — the provision of videos of people with stroke telling “inspiring stories” about their own stroke recovery — but as this study did not suggest any benefit from the inspiring stories compared to a wait list control or to the Take Charge intervention alone, this addition was subsequently dropped.

Based on this first successful clinical trial, a plan for a second fully powered study with a different stroke population was developed and implemented.<sup>34, 35</sup> Both clinical trials of this intervention (involving 572 participants combined) provided evidence of positive effects on physical health, functional activity, and independence, which were sustained at 12 months after stroke. Analysis of secondary data was used to further explore the psychological mechanisms by which the Take Charge intervention achieved its effects.<sup>36</sup> Authors of the Take Charge intervention used their experiences of delivery and study of the intervention to better explain how the intervention worked and for

whom, and to more clearly identify the key elements of the interventions.<sup>35, 36</sup> An economic analysis of the Take Charge intervention provided support for an argument that the cost of the invention may pay for itself in terms of improvements in functional independence and quality of life, and in lower need for rehospitalization or residential placement.<sup>37</sup> Subsequent applications of these ideas and a clinical trial of the Take Charge intervention has now been applied to a different population of people — those with chronic obstructive lung disease.<sup>38-40</sup>

Knowledge about the key ingredients of the Take Charge intervention and their theoretical mechanisms of effect are essential for implementation of this intervention in other clinical settings. The Take Charge intervention now explicitly draws on self-determination theory in addition to social cognitive theory, with an emphasis on autonomy, connectedness, purpose, and mastery.<sup>35, 36</sup> Replication of the Take Charge intervention is unlikely to reproduce the same positive results if the intervention is delivered at a patient’s bedside in a busy hospital ward, as a brochure rather than a conversation, or if a health professional were to take control over decisions regarding the goals a person with stroke should work towards when applying the intervention. Further work is arguably still required to study the

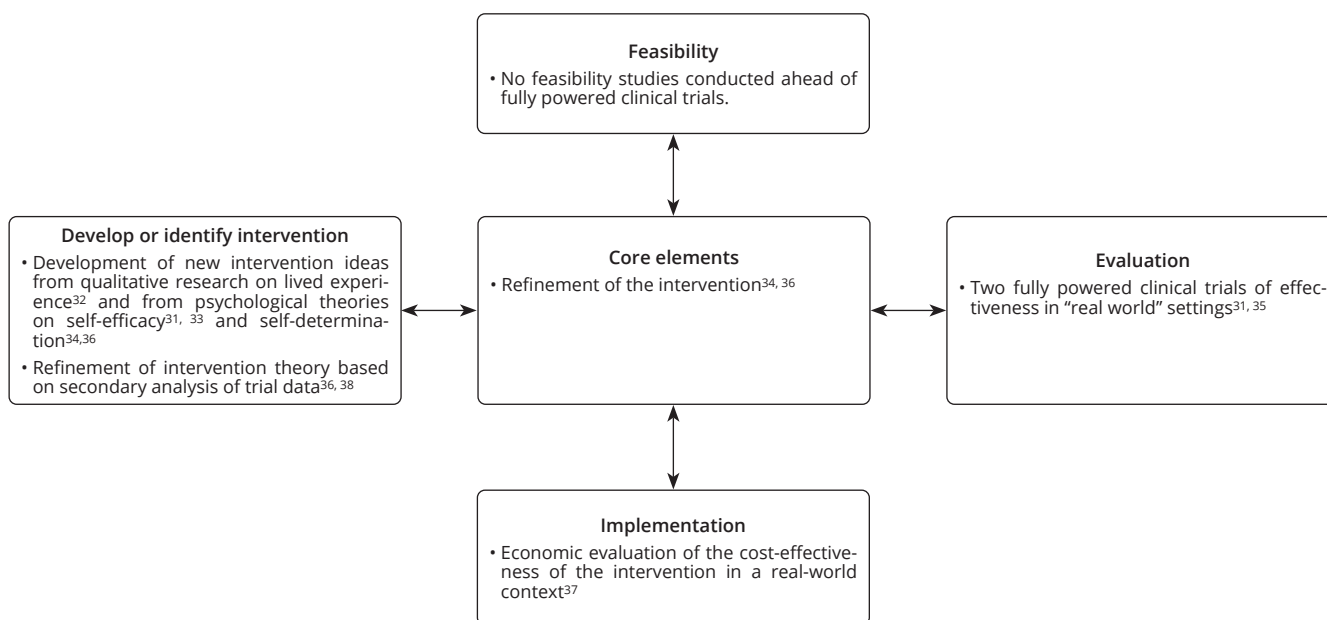


Figure 2.—Mapping research on the Take Charge intervention after stroke against the MRC-NIHR framework for developing and evaluating complex interventions.

rollout of this approach at a wider, national service level, with questions about how best to maintain intervention fidelity or train a workforce to deliver this intervention. An overview of how this research fits within the MRC-NIHR framework for development and evaluation of complex interventions as presented in Figure 2.

### Future challenges and implications for rehabilitation research

There is much that could be gained from greater engagement by the rehabilitation community in MCR-NIHR’s work on development of guidelines for research into complex interventions. Not only could rehabilitation research be strengthened by increased uptake of the MCR-NIHR’s framework and tools for implementation, but clinical practice in rehabilitation provides a fertile environment to further explore and develop this framework and related methods. Recommendations for rehabilitation researchers include that they should:

- familiarize themselves with the MCR-NIHR’s full report on the revised framework for development and evaluation of complex interventions;<sup>5</sup>
- use the MCR-NIHR’s framework to map their current and past work in the development and testing of specific complex rehabilitation programs;
- undertake studies to develop better understandings

of the organizational systems in which rehabilitation programs are delivered;

- proactively engage community partners, particularly people with lived experience of disability and their families, in the co-design of interventions and the development of implementation strategies and study design;
- systematically identify and report on key uncertainties related to rehabilitation programs prior to designing or undertaking studies;
- use these key uncertainties to guide future study design decisions, including decisions about which phase of the MRC-NIHR framework need take prominence in the next stage of development or testing of a particular complex intervention;
- develop and test of assumptions and theories about how rehabilitation programs work, for whom, and under what conditions;
- apply research methods designed to explore or test the implementation of complex interventions in everyday practice;
- apply research methods designed to better understand the impact of organizational, environmental, social, or cultural contexts on the delivery or impact of interventions in the field of rehabilitation.

All these recommendations also require an active engagement of funders to commission and support studies of complex rehabilitation interventions, particular if the



health sector is to achieve the goals the World Health Assembly resolution on “strengthening rehabilitation in health systems.”<sup>41</sup>

There are multiple resources that researchers may use to develop their knowledge and skills in these areas. The full report on the MCR-NIHR guidelines provides a list of key elements to be considered at the end of each phase of their framework and links to several resources to support its application.<sup>5</sup> In Table II<sup>5, 42-48</sup> we also provide a selection of

published tools that have been recommended for use in the development or implementation of evidence related to complex interventions. Each of these tools serves different but related functions, and work needs to be undertaken to determine which are more likely to be beneficial in furthering the development of evidence-based practice in rehabilitation contexts. All these tools are largely in the early stages of testing and application, which means that the research on them is still very much exploratory. Learn-

TABLE II.—Tools for aiding development or interpretation of research methods to study complex interventions.<sup>5, 42-48</sup>

Tool	Purpose	Structure and operation
MRC-NIHR’s checklist for developing and evaluation complex interventions (Appendix 6 of the MRC-NIHR’s guidelines) <sup>5</sup>	To guide preparation of funding applications, protocol design, and journal publication on studies of complex interventions – or for critical appraisal of such applications, protocols or published studies.	A 15-item checklist of binary (yes/no) criteria, covering the six core elements the MRC-NIHR guideline (addressing uncertainties, engaging stakeholders, considering context, developing and refining program theory, refining the intervention, and economic considerations) plus five optional phase-specific considerations.
Pragmatic Explanator Continuum Indicator Summary-2 (PRECIS-2) <sup>43</sup>	To guide trial design to align more with pragmatic (real world) versus explanatory (tightly controlled) study objectives.	A tool that scores trial design along a 5-point continuum from very explanatory to very pragmatic, across nine domains (eligibility criteria, recruitment, setting, organization, flexibility — delivery, flexibility — adherence, follow-up, primary outcome, and primary analysis). The tool produces a graphic representation of this data in the shape of wheel, rather than a single score.
Context and Implementation of Complex Intervention (CICI) framework <sup>44</sup>	To guide the conceptualization and assessment of context, implementation, and setting associated with complex intervention delivery.	A framework comprised of three dimensions: 1) The context dimension, comprised of seven domains (geographical, epidemiological, socio-cultural, socio-economic, ethical, legal, and political), 2) the implementation dimension, comprised of five domains (theory, process, strategies, agents, and outcomes), and 3) the setting dimension, where context and implementation interact. No scores are provided — instead, the framework is intended to structure and guide thinking.
Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare – revised (CRDeCI 2) <sup>45</sup>	To guide reporting on the development and evaluation of complex intervention.	A 13-item checklist of binary (yes/no) criteria, covering three stages of complex intervention development and evaluation (development, feasibility and piloting, and evaluation).
WHO-INTEGRATE <sup>46</sup>	To facilitate reflection and discussion on implementation evidence to practice, with an emphasis on complex interventions.	An evidence-to-decision framework comprised of six criteria derived from World Health Organization values and norms (balance of health benefits and harms, human rights and sociocultural acceptability, health equity, equality and non-discrimination, societal implications, financial and economic considerations, and feasibility and health system considerations) with a seventh meta-criteria (quality of evidence) applied to all other criteria. This framework can be applied at an individual, population or system level. No scores are provided — instead, the framework is intended to structure and guide thinking.
Intervention Complexity Assessment Tool for Systematic Reviews (iCAT-SR) <sup>42</sup>	To assess and categorize levels of intervention complexity in order to inform decisions regarding their inclusion and interpretation in systematic reviews.	An evaluation tool comprised of six core and four optional dimensions, with each dimension scored using a three or four level ordinal scale. The six core dimensions score the degree of complexity in the active treatment components, behavior of recipients, organizational levels, degree of tailoring intended, skill required delivery, and skills required by recipients. Dimensions scores are interpreted individually and not combined into a total score.
IDEAL-REHAB framework <sup>47</sup>	To provide guidance in the design and conduct of complex interventions in rehabilitation.	A five-stage guide that links steps in the development and evaluation of complex interventions to recommended research methods for answering core research questions at each stage. The five stages cover: idea formation, intervention development, exploration, assessment, and long-term outcome evaluation.
RE-AIM <sup>48</sup>	To provide guidance to program planners, evaluators, funders, and policy-makers in the sustainable implementation of evidence-based interventions, with a focus on complexity.	A five-stage step guide to translation of research into action and clinical practice, with each step including numerous dimensions, questions, and probes. The five stages cover: reach, effectiveness, adoption, implementation, aim maintenance. No scores are provided — instead, the framework is intended to structure and guide thinking.

ing which methods are best in which contexts to produce meaningful, impactful information will take some time and experimentation.

Several significant challenges remain regarding the future development of the concepts and methods proposed by the MRC-NIHR framework. There is inevitably a balance between appreciating complexity in its fullness and simplifying complexity in order to understand it. There is a risk that overly complicating evidence makes it impossible to be sure about anything. One example of this is the early implementation of the Intervention Complexity Assessment Tool for Systematic Reviews (iCAT-SR) — a tool for evaluating the degree of complexity of interventions when they are included and combined in a systematic review.<sup>42, 49</sup> A recent application of iCAT-SR to a systematic review on addressing polypharmacy in older people provided evidence for the high degree of variability in the degree of complexity of interventions to address polypharmacy across the 20 studies included in the review.<sup>50</sup> The included studies varied widely in terms of organizational structure, required behaviors or actions, number of active components, and level of permitted tailoring of the intervention — making it seemingly more confusing to compare or combine findings from studies included in this review. The authors also reported being unable to apply the “optional” elements of iCAT-SR due to insufficient information being reported on these domains in the included studies. As such, the authors questioned the value of continuing to use iCAT-SR in future updates of their review, recommending that study authors provide more details on the characteristics and features of their intervention so that intervention complexity could be better understood. The question is whether extensive additions to reporting requirements for clinical trials will help or hinder understanding of complexity in clinical practice.

## Conclusions

Complexity is an integral and unavoidable element of clinical rehabilitation, so needs to be taken into consideration when developing an evidence base for the field. The MRC-NIHR framework is the third iteration of a set of principles and guidelines for development and implementation of complex interventions, and therefore is directly relevant to all rehabilitation research. The authors of this framework advocate for the considered investment in and application of varied methodologies in addition to single RCTs in order to expand evidence-based practice beyond solely question of efficacy and effectiveness, to incorpo-

rate and address other questions relevant to the individualization and wider rollout of complex interventions in everyday practice. Rehabilitation research can both learn from and contribute to future iterations of this framework as it is an excellent environment for exploring complexity in clinical practice.

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*Conflicts of interest*

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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SUPPLEMENTARY DIGITAL MATERIAL 1

Supplementary Table I.—Strengths and weaknesses of different research methods in each phase of complex intervention development and evaluation.

Phase of complex intervention research	Relevant methods	Strengths	Weaknesses
Development or identification of the intervention	Literature reviews and broad scholarship	Aids in the identification of pre-existing theories on how existing interventions are thought to work. Minimizes the risk of unnecessary duplication of previous work.	Limits development of interventions to previously identified ideas and assumptions.
Development or identification of the intervention	Concept analyses	Aids in the development of clear and precise understandings of key concepts involved in an intervention, including how context and antecedents may contribute to changes in targeted outcomes. Minimizes the proliferation of different terminology for the same concepts, which might otherwise result in a confusing or disorganized evidence base.	Limits development of interventions to previously identified ideas and assumptions.
	Qualitative research*	Aids in the inductive development of new theories about the strategies or activities that may improve health and functioning for a target population and how these may work. Can draw on the lived experience of people with certain health conditions to develop these new ideas.	Theories arising from qualitative research may be limited to the specific context in which the study was conducted so have limited transferability to other environments or communities.
Feasibility	Feasibility clinical trials or pilot studies	Provides information on practical matters related to implementation of an intervention (e.g., cost, acceptability to study participants, "fit" with current clinical practices) or implementation of a fully powered clinical trial to evaluate it (e.g., recruitment rates, estimates of variance in	Should not be used to estimate the possible effect size of an intervention, due to lack of statistical power.

		primary outcome measures to inform power calculations).	
	Process evaluations within clinical trials	Aids in the refinement of theory regarding how an intervention works (i.e., the mechanism of effect) to inform revision to the intervention before conducting a fully powered clinical trial.	The process of delivery of an intervention within the context of a clinical trial may not reflect delivery of the same intervention in the context of real-world clinical settings.
Evaluation	Individual RCTs	Considered the gold standard method for evaluating the efficacy of experimental interventions. Are designed to maximize information about causal associations between an intervention and an outcome.	The complexity of an intervention, the diversity of people engaging in it, and the context in which it is delivered are all constrained to maximize internal validity. This limits generalizability of findings to broader, everyday clinical contexts.
	Cluster RCTs	Can be useful when interventions target behavior change at a group (e.g., organizational) level or when there is risk of contamination between intervention groups (e.g. people in a control group learning through observation or communication with people in an intervention group).	Dilution of effects if not all participants in each cluster engage in the experimental intervention. Increases in required sample sizes when taking baseline variability between clusters into account during power calculations, potentially making some cluster RCTs impractical to complete.
Evaluation or implementation	N-of-1 trials and realist evaluations	Provides detailed information about which interventions work best, for who, under what conditions. Can be used to refine treatment theory and provide theoretically informed guidelines for transferring or upscaling of interventions to other contexts.	Findings specific to intervention outcomes are related to the context in which a study was conducted – however, a theoretical understanding of mechanisms of effect contribute to the ability to generalize to other contexts. Multiple, serial evaluations may be needed to increase generalizability

			and further refine theories.
	Natural experiments	Permits evaluation of the effect of interventions in real world contexts, thus strengthening the external validity and generalizability of study findings. Can draw on data from large, historically collected data sets. Particularly useful when random assignment of participants to treatment groups is considered impractical or unethical.	Greatly increases external validity at the expense of internal validity. Selective exposure to interventions introduces bias and lack of reliable data on possible confounding variables, reducing confidence in causal inferences.
	Qualitative comparative analysis	Supports mixed methods approaches to evaluation of factors associated with improving outcomes for target groups of people. Allows for equifinality in evaluation of causation of outcome, i.e. that the same outcomes can be achieved via different pathways rather than requiring an intervention to have a single causal mechanism of effect.	Findings can be strongly influenced by the selection of cases and conditions that are included in the analysis, so findings may be predisposed toward pre-existing beliefs. Analysis often needs to be limited to a small number of cases and conditions for pragmatic reasons: time, cost, and feasibility of the analysis.

\*Qualitative research is a broad category of a range of research methodologies, each with their own strengths, weaknesses, objectives, and theoretical assumptions. These have been grouped together in this table for simplicity of expression.

## SUPPLEMENTARY DIGITAL MATERIAL 2

### Literature search

MEDLINE (Ovid) search strategy for rehabilitation articles that cite the MRC-NIHR guidelines or its predecessors.

1 ("journal of physiotherapy" or "journal of orthopaedic and sports physical therapy" or "journal of neuroengineering & rehabilitation" or "ieee transactions on neural systems & rehabilitation engineering" or "annals of physical & rehabilitation medicine" or "european journal of physical & rehabilitation medicine" or "disability & health journal" or "archives of physical medicine & rehabilitation" or "neurorehabilitation & neural repair" or "journal of neurologic physical therapy" or "journal of intellectual disability research" or "games for health journal" or "journal of rehabilitation medicine" or "brazilian journal of physical therapy" or "journal of occupational rehabilitation" or "career development and transition for exceptional individuals" or "physiotherapy" or "physical therapy" or "supportive care in cancer" or "research into development disabilities" or "american journal of speech-language pathology" or "journal of learning disabilities" or "clinical rehabilitation" or "american Journal of occupational therapy" or "exceptional children" or "rehabilitation psychology" or "journal of speech language and hearing research" or "american journal of speech-language pathology" or "journal of electromyography and kinesiology" or "research in autism spectrum disorders").jn

2 ("34593508" or "34590577" or "10987780" or "18824488").rz

3 1 and 2

Note: The suffix 'rz' is used in MEDLINE (Ovid) to identify articles that include reference to a specific article as indicated by a Cited Reference Unique Identifier (UI). Line 2 of this search strategy lists the UIs for latest version of the MRC-NIHR guidelines<sup>4,5</sup> and its predecessors.<sup>6,8</sup>