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Review

Current technology developments can improve the quality of research and level of evidence for rehabilitation interventions

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Abstract: Important current limitations of the implementation of Evidence-Based Practice (EBP) in the rehabilitation field are related to the validation process of new technologies and interventions. Indeed, most of the strict guidelines that have been developed for the validation of new drugs (i.e., double or triple blinded, strict control of the doses and intensity) cannot – or only partially – be applied in rehabilitation. Well powered high quality randomized controlled trials are more difficult to organize in rehabilitation (e.g., longer duration of the intervention in rehabilitation, more difficult to standardize the intervention compared to drugs' validation studies, limited funding's since not sponsorized by big pharma companies), which reduces the possibility of conducting systematic reviews and meta-analyses, as currently high level of evidence is sparse. The current limitations of EBP in rehabilitation are presented in this paper and innovative solutions are suggested such as: technology-supported rehabilitation systems, continuous assessment, pragmatic trials, rehabilitation treatment specification systems, and advanced statistical methods, to tackle the limitations to increase the quality of the research in rehabilitation. The development and implementation of new technologies should increase the quality of research and the level of evidence supporting rehabilitation provided some adaptation in our research methodology.

Keywords: Rehabilitation; new technology; validation; study design; methods

1. Introduction

For centuries the practice of medicine was based on clinical judgment and doctors' intuition rather than on scientific evidence. At this time, medicine was referred to as an art - *'the art of Medicine'* - rather than a Science. In the 1960s, thanks to the development of modern research, the amount of data was growing, and some researchers, led by Alvan Feinstein, started to challenge the way medicine was performed and brought the risk of bias under the attention that could affect clinical judgment [1]. A few years later, Archie Cochrane highlighted the lack of scientific evidence supporting the practices and treatment commonly used [2]. He called for an international register of randomized controlled trials, and for explicit quality criteria for appraising published research. The '*evidence-based medicine*' (EBM) slowly started to emerge, and the practice was now quickly evolving. EBM was defined as *'a systemic approach to analyze published research as the basis of clinical decision making'*[3]. Although the awareness of the importance of basing clinical decisions on strong scientific evidence began years before, the use of EBM started in clinics in the 1990s. The development of EBM, and the modification of patients' management, cannot be detached from the development of modern and clinical epidemiology [4].

The cornerstones of EBM are, still – currently - the Randomized Controlled Trials (RCT), which are the studies with the highest level of evidence [5]. However, these studies have some limitations: they are expensive and time-consuming since many patients need to be included to reach enough statistical power and lower the risk of bias [6].

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On the other hand, over the last years, there have been significant advances and developments in modern epidemiology, in medicine (i.e., genetics and immunology in medicine), and in rehabilitation with the growing development of new technologies (e.g., sensor based assessment, robotics, virtual reality, brain stimulation, etc.) allowing for objective measurements and technology-supported rehabilitation.

RCTs are currently not fully adapted to the development of precision therapy (i.e., personalized rehabilitation programs) or are difficult to put in place quickly in the context of emerging infectious diseases (e.g., the Covid-19 pandemic) [7]. EBM has become the benchmark for medical intervention, and today it is increasingly the benchmark for other healthcare professions. That is why we now prefer to use the term Evidence-Based Practice (EBP). For a healthcare provider, regardless of its activity, EBP is the combination of three elements [8]: 1) the provider's own clinical expertise, 2) scientific evidence, usually in the form of practise guidelines, and 3) the preferences and values of each individual patient. However, currently, the concept of EBP has only been partially transferred to physical rehabilitation, and most rehabilitation interventions are only corroborated by a low level of evidence.

Therefore, this paper aims to summarize the different study designs currently available in rehabilitation research and discuss their limitations. Limitations and future perspectives of EBP are also discussed in the context of current research in rehabilitation.

2. Current situation and limitations of the research and its translation to the care

2.1. Study design and level of evidence

The traditional flow of development and the different validation steps of a new treatment are presented in Figure 1 (adapted from the drug development pipeline since these numbers are not available for the development of new interventions or of technology in rehabilitation) [9]. It is interesting to note the very large number of participants (healthy subjects and then patients) required to carry out the various stages of clinical validation, as well as the length of time between the development of a product and its launch on the market. The different study designs and their level of evidence are presented in Figure 2. Although some authors question this pyramid [10], the different levels of evidence on which EBP is based are generally well accepted in research and in clinical practice.

Concerning drug validation, RCTs are requested by the authorities before starting discussions on the marketing of the new molecule. In the past, the new treatment had to be more efficient (superiority trial) than a placebo (i.e., sham treatment without active substance). However, when treatment is already available (gold-standard), it is unethical to deprive half of the participants of a study of this treatment [11] Therefore, currently, in the presence of a gold standard, the common practice is to perform equivalence or non-inferiority trials to compare the efficacy of the new drug against this gold-standard [12]. From a statistical point of view, there are some differences, but methodologically the critical point is the randomization. The randomization allows to get rid of some potential confounding factors but having randomization does not mean that a study is not biased. In the next part, we will discuss the main limitations of RCTs and the sources of error in medical research [13] and thus of the meta-analysis that derives from it [14].

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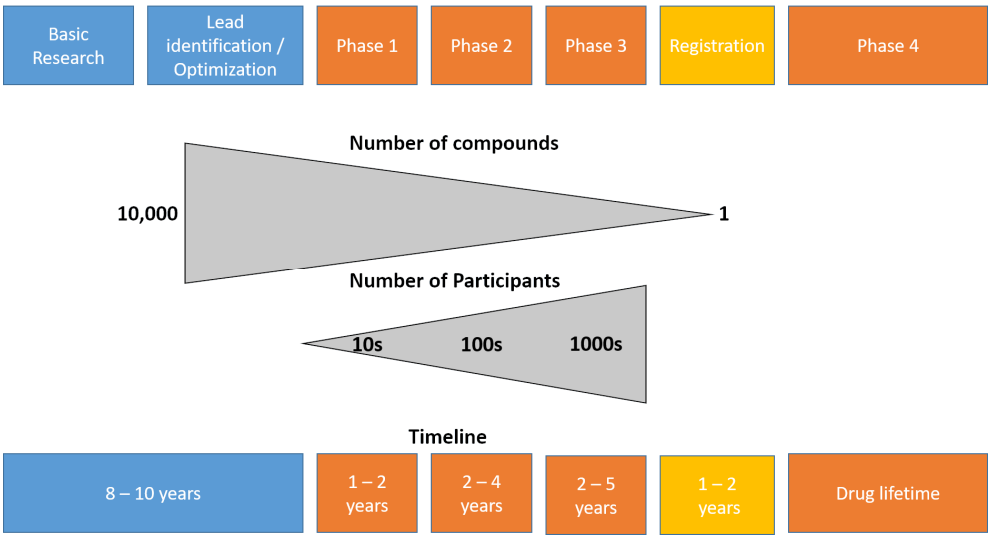

Figure 1. The rocket model, adapted from Verweij et al. 2019 [9]. Note that this model and numbers come from the development of new drugs as no data are available for new interventions in rehabilitation sciences. Blue colors indicate the different steps of the discovery, development and preclinical research, orange color for the clinical development. The different steps of the clinical development are: Phase 1 – Healthy Volunteer study: This is the first time the drugs is tested in people; less than 100 volunteers are usually involved, the pharmacokinetics, absorption, metabolism, and excretion effects on the body, as well as any adverse effects associated with safe dose ranges will be determined. Phase 2 – Small sample size study in patient population: evaluates the safety and effectiveness of the medicine in an additional 100–500 patients who may receive a placebo or a previously utilized standard of care. The analysis of the ideal dosage strength aids in the development of schedules, while adverse events and dangers are documented. Phase 3 – Large scale clinical study: typically enrolls 1,000–5,000 patients, allowing medication labeling and adequate drug usage instructions. Phase III studies need substantial cooperation, planning, and coordination and control by an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) in preparation for full-scale manufacturing after medication approval.

2.2. Challenges in validation of new intervention and suggestions for reconsideration of the choice of the outcomes

The complexity and challenge of the validation of a new intervention can be summarized in two constraints: time and cost, that will lead to various challenges: small sample size and low statistical power, bias, and low external validity of the studies.

Most of the time and financial resources are deployed during the phase 3 of the clinical development (see Figure 1 for the different steps, phases, and their definitions). We present the different study designs according to the time and money needed to perform them in Figure 3. Because they required strict control, regular testing (e.g., biological testing, imaging, functional assessment), and many patients to have sufficient statistical power, the RCTs are - by far - the most expensive studies. As an example, again from the pharma world since these numbers are not known in the rehabilitation sciences, in the USA, the average cost of a Phase 1 study (healthy volunteers study) ranged from US$1.4 million (pain and anaesthesia) to US$6.6 million (immunomodulation), including estimated site overhead and monitoring costs of the sponsoring organization. A Phase 2 study (small sample size study in patient population) costs from US$7.0 million (cardiovascular) to US$19.6 million (haematology), whereas a Phase 3 study (large scale clinical study) cost ranged from US$11.5 million (dermatology) to US$52.9 (pain and anaesthesia) on average.[15] Therefore such studies cannot be conducted without sponsors, mainly the pharmaceutical companies, which can lead to a conflict of interest [16]. In the wake of numerous scandals that have warred the scientific community [17], clinical trial governance frameworks have been developed for pharmaceutical industry-funded clinical trials [18]. However, the recent retractions of studies about COVID-19 treatments have highlighted

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the existing relationships between researchers, private companies, and scientific journals leading to public mistrust of the independence of research. Furthermore, several studies have found a significant association between funding sources and pro-industry conclusions [19].

Another issue is the sample size needed to complete these studies. In the case of rare, or very rare diseases, it is sometimes impossible to recruit enough patients in a RCT to reach the statistical power.[20] It has been for example clearly shown that lack of statistical power is one of the main limitations of current research in neuroscience,[21] but the situation is exactly the same in the field of rehabilitation.[22] In addition to the small number of subjects included in the studies, intention to treat analysis is not always straightforward in rehabilitation (e.g., loss in follow-up, change of rehabilitation strategies according to the evolution of the patients through the rehabilitation process and its specific needs)[23]. This point may weaken the power of individuals studies and of RCTs. While RCTs in all (para)medical specialties are subject to loss to follow-up, rehabilitation trials have an especially poor track record of both reporting loss to follow-up and attaining adequate follow-up. As a result, minimizing follow-up loss should become a critical methodological priority in rehabilitation research.

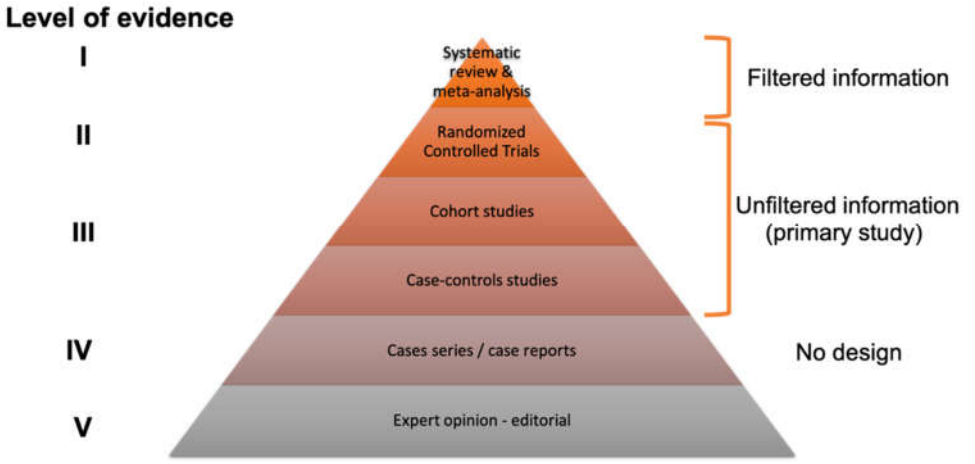

Figure 2. Study design and level of evidence [14]. This pyramid may be more detailed, but the general idea is to separate four kinds of studies: the meta-analysis of published studies on the top (e.g., systematic review and meta-analysis), as level I evidence. Then the experimental studies: fully controlled (RCT) and pseudo-RCT (level II); quasi-experimental designs (i.e., prospective studies). The observational large-scale studies: cohort studies and case-control studies (level III) and the case reports or case series are at the base of the pyramid with a low level of evidence (level IV). Finally, the expert opinion, not based on any scientific data or evidence, presents the lowest level of evidence (level V).

We have seen that RCTs are the interventional studies with the highest level of evidence. However, the results are not always reliable and unbiased.[24] Strict guidelines have been developed to increase the quality of the study and decrease the risk of bias.[25] The protocol must be strictly followed, the allocation, the treatment, and the assessment should be performed blinded and ideally, the blind statistical analysis should be carried out by an external team. Adhering to these measures ensures that the results of the study can be thrusted (internal validity). These parameters are, however, rather difficult to implement in rehabilitation research. In rehabilitation research, the blinding of the patients or the therapists is not always possible. Also, one of the specificities of rehabilitation is to propose a personalized treatment adapted as much as possible to the specificities and needs of the patient, in clinic the treatment is therefore very often not fixed in time. For these reasons treatment is often referred to as the 'black box of rehabilitation' [26,27]. This lack of precise definitions, standardization and specifications of the interventions used in the studies [28] is responsible for a lack of replicability in RCTs in rehabilitation [29], and

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this has limited the establishment and synthesis of evidence-based practice in rehabilitation [30].

Furthermore there are also some discrepancies between the results of RCTs and real-life results [31]. Two mains reasons explain this (external validity): the treatment adherence is lower in real-life compared to the strict and controlled RCT environment [32], the second point is the selection bias (or representative bias) [33]. It is well known that patients participating in clinical trials are not representative of the total patients' population [34]. For example in asthma and chronic obstructive pulmonary disease, RCTs often represent only a minority (5 to 10%) of the routine care population in whom licensed interventions will be applied [35].

A last important limitation of the research in rehabilitation, which is particularly important in the validation of new technologies, is the very important development speed of these technologies. We have seen that the validation process is time consuming, therefore some validations studies are only available when the device may already be outdated due to limited sustainability (e.g., mobile applications).

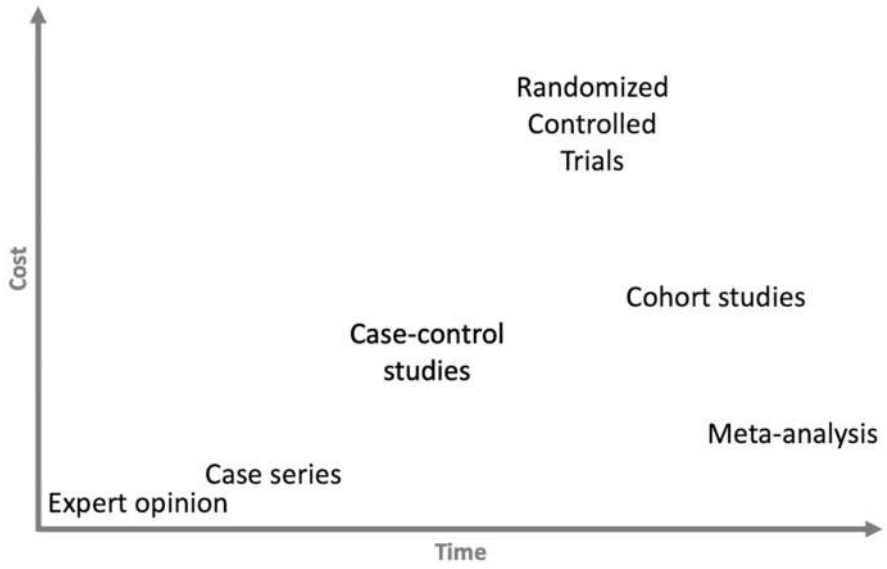

Figure 3. Relationship between time and cost of the different study design.

Combining the results of different studies in meta-analysis helps to address, partially, the external validity issues (multiple clinical centers involved, different populations, different teams of clinicians, etc.), but above all increases the statistical power by increasing the number of participants [36]. It is worth mentioning here that one should distinguish between the statistically significant differences (that can be achieved with the inclusion of more patients), and the clinical relevance of the observed difference (independent of the sample size) [37]. Unfortunately, although they offer the highest level of evidence, it does not mean that the conclusions of meta-analyses cannot be biased [24]. There are two main sources of bias that could influence the results of a meta-analysis. The first one is selection bias [38]: if not all the published studies are analyzed; the final results will not represent the real situation; this point depends on the quality of the systematic review performed. The second is the publication bias or reporting bias: it describes aspects of a phenomenon by which certain data from trials are not published, and so remain inaccessible [39]. It is well known that studies with statistically significant results have increased likelihood of being published, publication bias is commonly associated with inflated treatment effect which lowers the certainty of decision-makers about the evidence [40]. We will discuss in the next part how to deal with this phenomenon and evaluate the direction and magnitude of this bias.

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3. New developments allow for innovative clinical trials

In the first part, we inventoried challenges inherent to RCTs and meta-analyses. In this section, we aim to discuss new developments and techniques that could on the one hand be used to speed up research by decreasing the number of participants required, reduce the time of studies if necessary and allow a better allocation of human and financial resources [41], and reduce uncertainty, on the other hand.

3.1. Innovative technologies to facilitate high quality clinical trials

Rehabilitation may be aided by one or more existing technologies such as robotics, muscle and brain stimulation, sensors based- exergames, virtual reality [46]. Recent years have seen an increase in the use of robot-mediated treatment in rehabilitation to offer highly adaptable, repetitive, rigorous, and quantified physical exercise [47]. Therefore, the development of technology-supported innovative rehabilitation solutions appears to be a promising way to solve the above mentioned limitation of current research in rehabilitation namely lack of statistical power due to small sample size and a choice of clinical outcomes not sensitive enough to detect small changes and a lack of continuous assessment and evaluation. Technology-supported rehabilitation, has gained appeal due to the ability to give an objective and if necessary blinded assessment, that can be automated (time saver) and allows for measurable evaluation of motor function by taking into account the characteristics of the patients (e.g., kinematics, activity level, intensity, muscle activity, co-contraction, posture, smoothness, heart rate, stress level, etc.) and of therapy adherence [47]. Most of the devices indeed allow for the continuous recording of the motions performed by the patients during the rehabilitation exercises [48,49], those analyses could be used later on to adapt the dose and intensity at an earlier stage of the research or to decide to stop an intervention if it is turns out that the patient cannot benefit from it [50]. Another salient aspect of the use of new technology in rehabilitation is the remote monitoring of the patients between the sessions during the activities of daily living. Mobile health technologies (wearable, portable, body-fixed sensors, or home-integrated devices) that measure mobility in unsupervised, everyday living situations are indeed gaining traction as adjunctive clinical evaluations. Due to the fact that data acquired in these ecologically valid, patient-relevant contexts capture variable and unusual occurrences, they may overcome the constraints of standard clinical examinations [51]. Future development must focus on the integration of the information from the rehabilitation and the unsupervised assessment to better evaluate the efficacy of rehabilitation intervention.

3.2. Adaptative trials

In the past, patients' allocation in RCTs was equal in the different groups and the study went on until the end (i.e., the inclusion and follow-up of the required number of patients). This posed two majors' threats: it does not allow to stop the study in the event of a higher occurrence of side effects in the treated group, or in the event of a more favourable evolution in the treated group, in which case it is unethical to continue giving non-effective treatment to half of the subjects included in the study. Interim analysis, an analysis performed during the study, has been proposed to avoid these situations [42]. Interim analysis may also be used to adapt the required sample size based on the current results or stop the study if the revised sample size is deemed to be unfeasible [43]. Finally, the adaptive trial design has been proposed as a means to increase the efficiency of RCTs [44], being more flexible than interim analysis. It has multiple advantages for both the patients (increasing the odds of benefiting from the treatment) and the researchers (reducing the cost and increasing the speed) while increasing the likelihood of finding a real benefit [45]. Different adaptative trials have been developed, suited for both Phase 2 (e.g., effective doses and dose-responses modelling) and Phase 3 trials. The adaptive nomenclature refers to making prospectively planned changes to the future course of an ongoing trial based on an analysis of accumulating data from the trial itself, in a fully blinded or unblinded manner, without undermining the statistical validity of the conclusions [44].

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In rehabilitation, to the authors best knowledge, this type of study design is not implemented yet.

3.3. Advanced statistical methods to increase the efficiency of the research

Adaptative trials rely on the development of robust intermediate or continuous statistical analysis. New methods such as Bayesian adaptative designs [52], or deep learning [53] are also used in development to increase the follow-up and allow for quicker modification of trial designs in order to speed up the process and to allow a maximum number of patients to benefit from the best treatment while guaranteeing the power necessary for the study. Describing these different methods is beyond the scope of this article, but we could not discuss adaptative trials without at least mentioning the development of the statistical method. Indeed, changes in the design of the studies are made after the analyses carried out by the statisticians (most of the time, external companies analysing the results blindly). The development of data sciences and the implementation of the new techniques in the field of rehabilitation also opens new perspective for a most agile adaptation of the treatment, ultimately leading to precision treatment [50]. We have previously seen that, currently, personalized treatment conflicts with strict protocols for RCTs. If the personalization uses the same algorithms for all participants, it is protocolized and not in conflict with RCT set ups anymore.

Concerning the meta-analysis, the two main biases were the selection bias and the publication bias. For the selection bias, researchers are working on automated methods (e.g., text mining) that could improve and speed up the selection of the studies, but such method is still under development. On the other hand, concerning publication bias, the statistical method (i.e., trim and fill method) has been developed to estimate the size of the effect and to correct it [54]. Bayesian methods can also be used to minimize this bias.

4. Perspectives on the development of scientific evidence in rehabilitation

The goal of clinical research is to improve the health and quality of life of the patients. For this, EBP has been developed to guide practitioners in their daily practice and to ensure that they integrate the latest research optimally into their treatments. In this last part, we are going to discuss how to ease and increase the translation between research and clinical practice, focusing on pragmatic trials and the development of the rehabilitation treatment specification system.

4.1. Pragmatic trials

As stated above, one of the most significant limitations of RCTs is the weak translation between research results and clinical reality [31]. The two main limitations of the translation are the treatment adherence, much lower in real-clinical conditions compared to RCTs, and the representativeness of the population participating in the RCTs.

Improving treatment adherence may have a more significant influence on the health of our population than the discovery of any new therapy [55]. Although the factors favouring or, on the contrary, hindering the treatment are well identified, it is estimated that patients are nonadherent to their treatment 50% of the time [55]. In rehabilitation this problem occurs only for the exercises that the patients need to perform at-home between the session under the supervision of the physiotherapists [56]. Solutions are being developed to increase the adherence through decreasing the frequency of face to face sessions [57], motivational interviews [58], and smartphone applications that support treatment instruction, that track adherence, provide patients' education and provide feedback on performance [59]. To be closer to clinical reality, some studies can be performed in real-life conditions. Although closer to reality, the problem with this type of approach is that it risks losing the well-controlled aspect that is specific to RCTs, another limitation is that due to larger heterogeneity in participants or interventions, larger sample sizes are often needed compared to well controlled RCTs [60]. To combine both the positive aspects of

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RCTs and the real-world data some authors suggested to use a hybrid approach using randomisation coupled with the use of pragmatic outcomes [61].

Thanks to the development of technologies, home-based assessment, and monitoring are becoming popular in research and practice [62], and smart homes can be used to collect medical data that can be used for follow-up and monitoring RCTs [63]. In addition to allowing a quick response in case of detection of abnormal values, such kind of approach also allows to collect a huge amount of data that could be used for machine learning to find more sensitive outcomes.

The second limitation, the lack of representativeness of the patients included in the studies, is trickier to handle. Most of the research is performed in university hospitals, representing only a specific part of the population [64]. The problem of access to care is highly multidimensional including not only financial resources but also health literacy, social support, the representation of the disease, etc [65].

4.2. Rehabilitation Treatment Specification System

Although significant advances have been made in measuring the outcomes of rehabilitation interventions, comparably less progress has been made in measuring the treatment processes that lead to improved outcomes [66]. The field of rehabilitation remains captive to the black-box problem: the inability to characterize treatments in a systematic fashion across diagnoses, settings, and disciplines, so as to identify and disseminate the active ingredients of those treatments [67]. Rigorous definition of rehabilitation treatments, supported by theory, has been proposed in the framework of the Rehabilitation Treatment Specification System (RTSS) [66]. In the future, accurate measurements of the dose and intensity should be integrated within the RTSS to be more close to real-clinical case to improve the reporting, as these parameters are crucial in the rehabilitation [68].

5. Call for action: the development of Evidence-Based technology supported Rehabilitation

Although EBP is the current trend in health care practice, some clinicians and physicians are above all focused on the limitations of this approach (i.e., overall reductionism). According to them, EBP does not represent the scientific approach to health and care: it is only a restrictive interpretation of the scientific approach to clinical practice [69]. Another major limitation pointed out by some authors is the dehumanization of the patients, which are reduced to a set of numbers without taking into account social and human aspects [70]. The development and implementation of the International Classification of Functioning, Disability and Health (ICF) in rehabilitation, at least in research, is no longer in question [71]. However, while in clinics clinicians try to integrate the different components in the treatment and to adapt the treatments from session to session, in research we are still miles away from the concept of personalized or precision rehabilitation [72]. The concept of personalized rehabilitation is closely associated with the black box rehabilitation [73]. We have seen that this is, currently, one limitation of the replication of the studies in rehabilitation. However, the latest and most advanced statistical methods allow new perspectives in the management of the black box rehabilitation. One of the prerequisites of this analysis is to describe as precisely as possible the different interventions and techniques used – using for example the RTSS framework including the dose and intensity, and the outcomes using the ICF. The different components of the black box could then be analyzed individually to assess their specific effects. These approaches will also allow to identify which patients are the most likely to benefit from a certain intervention in a certain moment of the rehabilitation process. Currently, most of the physiotherapists perceive EBP as useful and necessary but it is important to note that there is gap between perceived and actual knowledge of EBP [74]. We think that if we improve the EBP by integrating the different components in there, the clinicians would be more likely to support it and use it in their practice. It is also important to teach the clinicians about the importance of this process [75].

6. Conclusion

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Although RCTs have been, and still are, considered to be the most robust studies in clinics, we have seen that they present risk of bias, just like the meta-analysis, and are sometimes difficult to apply in the rehabilitation field. To decrease some of the weakness of the RCTs, mainly the length of the study and the number of patients needed, adaptative trials have been developed and are increasingly used in medical research but not yet, or only to a very limited extent, in the field of rehabilitation. The development of technology-supported rehabilitation offers unique perspectives to monitor the evolution of the patients during the rehabilitation process. The data collected should be used to increase the quality of the trial by allowing blinding of assessors and automated and standardized data collection, of the reporting and therefore the quality of the evidence.

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