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Systematic Literature Review

# The Value of Nonpharmacological Interventions for People With an Acquired Brain Injury: A Systematic Review of Economic Evaluations

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## ABSTRACT

*Objectives:* Acquired brain injury (ABI) has long-lasting effects, and patients and their families require continued care and support, often for the rest of their lives. For many individuals living with an ABI disorder, nonpharmacological rehabilitation treatment care has become increasingly important care component and relevant for informed healthcare decision making. Our study aimed to appraise economic evidence on the cost-effectiveness of nonpharmacological interventions for individuals living with an ABI.

*Methods:* This systematic review was registered in PROSPERO (CRD42020187469), and a protocol article was subject to peer review. Searches were conducted across several databases for articles published from inception to 2021. Study quality was assessed according the Consolidated Health Economic Evaluation Reporting Standards checklist and Population, Intervention, Control, and Outcomes criteria.

*Results:* Of the 3772 articles reviewed 41 publications met the inclusion criteria. There was a considerable heterogeneity in methodological approaches, target populations, study time frames, and perspectives and comparators used. Keeping these issues in mind, we find that 4 multidisciplinary interventions studies concluded that fast-track specialized services were cheaper and more cost-effective than usual care, with cost savings ranging from £253 to £6063. In 3 neuropsychological studies, findings suggested that meditated therapy was more effective and saved money than usual care. In 4 early supported discharge studies, interventions were dominant over usual care, with cost savings ranging from £142 to £1760.

*Conclusions:* The cost-effectiveness evidence of different nonpharmacological rehabilitation treatments is scant. More robust evidence is needed to determine the value of these and other interventions across the ABI care pathway.

*Keywords:* acquired brain injury, economic evaluation, nonpharmacological interventions, stroke, systematic review.

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## Introduction

Worldwide, there is approximately 100 million people who have an acquired brain injury (ABI) disorder[1-3]; the prevalence of ABI and its costs will undoubtedly rise as the aging population increases.[2,4] ABI is the third most common cause of death and disability internationally and is becoming a major health and economic issue.[5,6]

Upon diagnosis of an ABI disorder, a variety of treatments have been proven to be clinically effective in slowing disease progression and managing symptoms.[7,8] In particular, nonpharmacological rehabilitation interventions have shown promising results, and the number of studies in this area for patients with ABI and their caregivers has been increasing in recent years.[9,10]

Current evidence-based guidelines are increasing recognizing the complexity of having an ABI.[11] Allocating resources to ABI rehabilitation care will mean policy makers having to forego some alternative healthcare decisions. The economic costs of having an ABI disorder are becoming an increasingly important parameter for health and research policies, but solid evidence-based estimates are lacking[5,12,13] and ABI research remains severely underfunded.[14] There is a scarcity of economic evidence regarding nonpharmacological interventions for ABI[15-17] and their informal caregivers.[15] Nevertheless, to inform resource allocation decisions, information on the effectiveness and cost-effectiveness of intervention strategies is essential for healthcare and governmental decision makers.[18] Additionally, to the best of our knowledge, systematic reviews of economic evaluations of nonpharmacological interventions have predominately focused solely on stroke patients. Therefore, an updated systematic review of nonpharmacological interventions with a broader approach including all types of ABI disorders is lacking, especially given the increased interest and concern for ABI disorders during the past decade. Hence, the aim of this study is to conduct a systematic review of economic evaluations of nonpharmacological interventions directly targeted at individuals with an ABI disorder.

## Methods

### Search Strategy

We conducted a systematic review to identify studies that had conducted an economic evaluation of nonpharmacological interventions for people with an ABI. Eligibility criteria for the selected studies in the review were determined by population, intervention, control, and outcomes (PICO) guidelines.[19] The PICO is an acronym term that refers to the Population, Intervention, Comparison, Outcomes and Study design of an ABI article. The population was limited to the adult population with an ABI. The term ABI encompasses both traumatic brain injuries (TBIs) (such as falls and motor vehicle crashes) and a nontraumatic cause (such as stroke and brain tumors).[20] ABI are injuries to the brain that is not hereditary, congenital, degenerative, or induced by birth trauma; it occurs after birth.[21]

The review included any nonpharmacological rehabilitation, that is, that aims to reduce, eliminate, or alleviate symptoms associated with having an ABI disorder. Studies had to include an economic evaluation such as cost minimization analysis, cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis. No limitations were placed on study setting or the time horizon adopted by economic evaluations. We excluded studies with no cost data attributable to ABI and non-English language studies, because of the lack of access to an interpreter. We excluded conference abstracts, protocol studies, unpublished or gray literature, posters, and studies without full-text available. The PICO criteria used in this review are displayed in (Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.03.014). The following databases were searched PubMed, CINAHL (EBSCO), MEDLINE (Ovid), Embase, PSYCinfo, Web of Science, EconLit, and NHS Economic Evaluation Database from inception to 2021. The reference lists of studies meeting inclusion criteria were also searched for additional related articles. A health information specialist with expert knowledge in systematic reviews was responsible for running the search strategies, which included Medical Subject Headings terms and text words. Searches of each database follow a similar structure: population terms and economic evaluation terms and modeling terms and limitation terms. A detailed search strategy including keywords is presented in the Supporting Information (Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.03.014) section. Unpublished or gray literature was not included. The search was limited to studies only in English.

### Study Selection

The identified records were independently screened at title and abstract level by 2 reviewers using the search strategy developed in consultation with the other authors. Two authors independently removed the duplicates manually. Furthermore, they reviewed all the titles independently, and any conflicts in article selection were resolved after mutual discussion with a third reviewer. Additionally, references lists of all included studies were also examined to identify any additional relevant studies. Finally, 2 reviewers independently reviewed and cross-checked the full texts of the included articles, and any disagreements were resolved through discussion with 2 other reviewers. This systematic review was registered with PROSPERO (registration number CRD42020187469).[22] A peer-reviewed protocol of this study was also published.[23]

### Data Extraction

Studies that met the inclusion criteria after the full-text review were assessed for quality by 2 authors using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist criteria.[24] Double data extraction was done by 2 authors from the eligible full articles. Any discrepancies were discussed and clarified with 2 other authors. The arbitrator reviewed any apparent discrepancies and made the final recommendation. Extracted information included record details (author, title, publication date, journal), study characteristics (trial design, analytical technique, intervention and comparator names and descriptions, primary clinical and economic outcome measure, time horizon, study perspective, cost categories, currency, price year), and relevant results of the studies. Information regarding the country where the study was conducted, study population type, and sample size were also noted. In cases when the incremental cost of ABI intervention was not reported, cost savings or outcome consequences of the intervention were instead reported. To allow for comparability between varying years and local currencies, reported costs were transferred from local currency in the year of the costs (if not stated, then in the year of publication) to the inflated values in local currency for the year 2020, for which the latest statistics are available.[25] To allow for international comparison of costs, country costs of ABI interventions were further exchanged to GBP sterling by using the gross domestic product purchasing power parity according to Organisation for Economic Co-operation and Development recommendations (with United Kingdom as a reference country).[26] Countries were classified as either high income or low income based on the World Bank atlas method.[27] Due to heterogeneity of the cost estimates and the lack of essential statistics, being reported (eg, standard error, variance, or confidence interval [CI]), a meta-analysis was not performed.

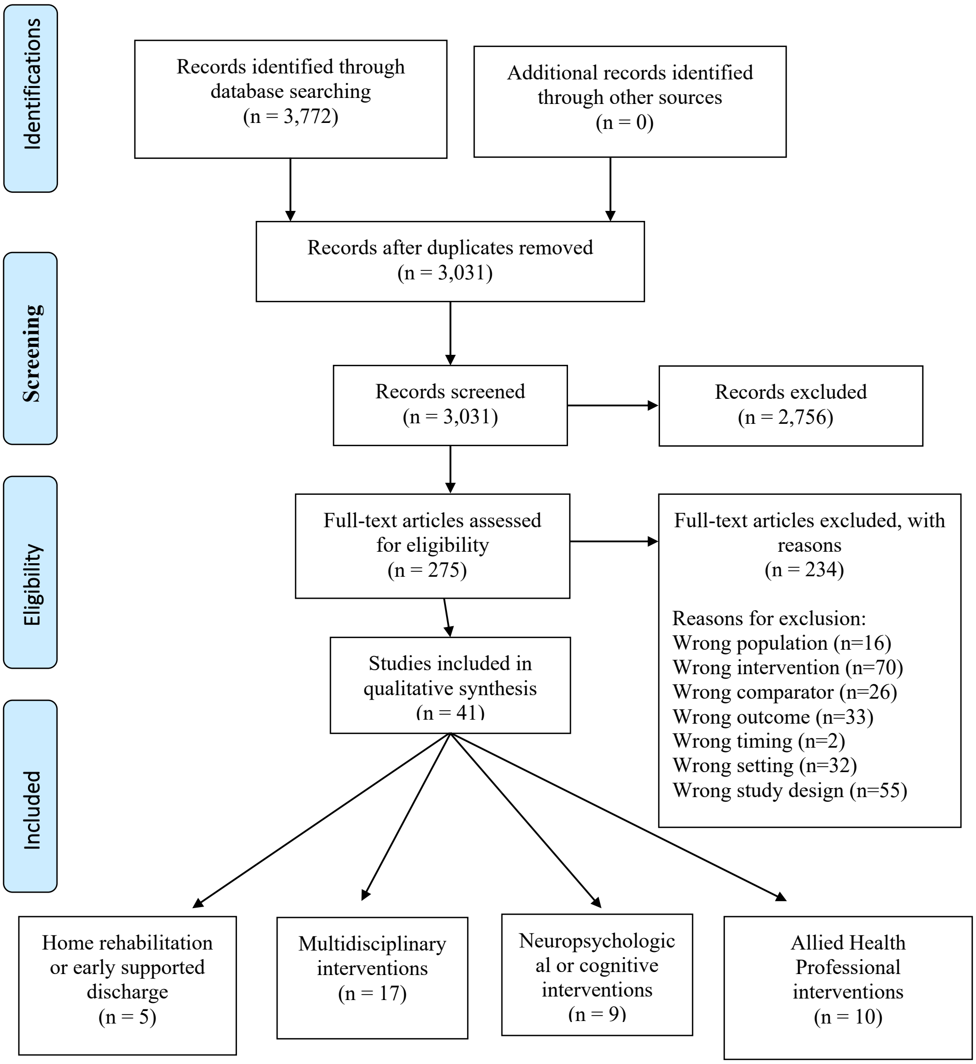
### Quality Appraisal

The quality of the economic evaluation was assessed using the CHEERS checklist criteria[24] and has been used extensively and is recommended in Cochrane reviews as a means of informing appraisal of the methodological quality of economic evaluations. The CHEERS guideline has 24 items in 6 categories (title and abstract, introduction, methods, results, discussion, and other). Each item of the CHEERS list was formulated as a question that can be answered by yes or no. The CHEERS list does not make provisions for the calculation of numerical scores that summarize a study's quality; therefore, no such scores were calculated. It should be noted that negative answers to checklist items do not necessarily concede poor practice or result in bias. Although no identified studies were discarded because of poor methodology quality, the limitations of these studies are discussed in the following section. Additionally, any available economic resource information was assessed using the Drummond Checklist[28] shown in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.03.014. This criterion was applied by a health economist to indicate the cost of the intervention and the consequences of the intervention on resources and costs relevant to various public sectors.

## Results

Our search strategy identified 3772 publications (Fig. 1). After removing duplicates and excluding for relevance, 41 economic evaluation studies, including randomized controlled trials (RCT)

**Figure 1.** PRISMA flowchart of the study selection process.




PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

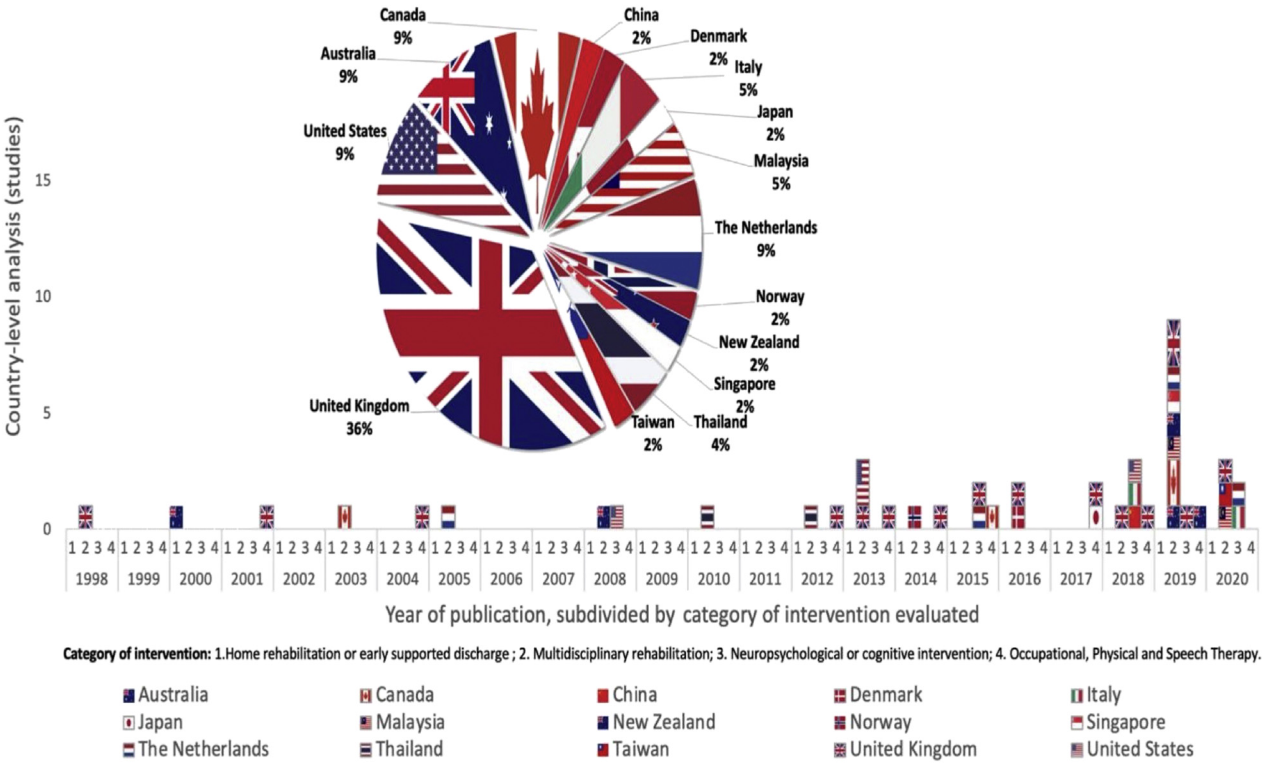
(58.5%), simulation models (19.5%), non-RCTs (14.6%), and cohort studies (7.3%), were fully abstracted and incorporated into the final analysis.

The earliest economic evaluation study was conducted in 1998; since then, economic evaluations of ABI have been rare (see Fig. 2). Overall, contribution to improving our knowledge on improving economic implication of ABI has come from 15 countries (Australia, 4; Canada, 4; China, 1; Denmark, 1; Italy, 2; Japan, 1; Malaysia, 2; The Netherlands, 4; Norway, 1; New Zealand, 1; Senegal, 1; Thailand, 2; Taiwan, 1; United Kingdom, 16; United States, 4). Among the 41 included studies, 37 (90.2%) were from high-income countries (eg, United Kingdom 39%, United States 7.3%, and Australia 12.2%) and 4 (9.8%) from low- to middle-income countries (eg, China 2.4%, Thailand 4.9%, and Malaysia 2.4%).

The characteristics of included studies are summarized in Table 1.[29-69] The studies reviewed evaluated a wide range of interventions, and the descriptions used in each of the included studies varied considerably. Interventions assessed in the identified studies were categorized into the following groups: (1) multidisciplinary inpatient or outpatient rehabilitation (n = 17 [41.5%]), (2) interventions to support and enhance neuropsychological or cognitive abilities in individuals with ABI such as cognitive stimulation (n = 9 [21.9%]), (3) allied health professional interventions (eg, occupational, physical, and speech therapy) (n = 10 [24.4%]), and (5) home rehabilitation or early supported discharge (ESD) intervention programs (n = 5, [21.9%]). A full breakdown of the studies is provided in Table 2.

Findings of each study, grouped according to the nature of the compared interventions, are given in the text below. Seventeen studies examining the cost-effectiveness of multidisciplinary interventions were identified. Multidisciplinary interventions included a range of interventions such as integrated rehabilitation services (n = 8),[29-36] extra rehabilitation care (n = 3),[37-39] rehabilitation team treatment, and fast-track specialized services (n = 6).[40-45] Fifteen studies were conducted in high-income countries (n = 1) in low-income country and (n = 1) in middle-income country. Thirteen studies focused on stroke on patients with TBI (n = 3) and ABI (n = 1). Seven multidisciplinary interventions studies were RCTs (n = 3), model (n = 2), cohort (n = 1), non-RCT (n = 4), and longitudinal study (n = 1). A total of 6 studies[29-32,34,35] involving integrated rehabilitation services reported cost savings

Figure 2. Contributions of countries (41 studies across 15 countries) toward knowledge toward improving the economic implications of acquired brain injury between 1998 and 2020, aggregated country contributions (pie chart), and country-specific contributions by year and subdivided by category of intervention evaluated (bar chart).




ranging from £632 to £10 987 (costs converted to price year 2020 sterling prices). A total of 3 studies[37-39] involving extra rehabilitation care reported cost savings ranging from £329 to £1889. A total of 4 studies[41-44] concluded that fast-track specialized services were cheaper and more cost-effective than usual care, with cost savings ranging from £253 to £6063 (costs converted to price year 2020 sterling prices). For instance, Grieve et al[41] found that "fast-track early" transfer to a neuroscience center was associated with lower mortality (odds ratio 0.52, 95% CI 0.34-0.80) and higher quality of life for survivors (mean gain 0.13, 95% CI 0.032-0.225) but positive incremental costs (£15 001, 95% CI £11 123-£18 880) compared with late or no transfer. The cost-effectiveness acceptability curve showed 60% probability to be cost-effective at £20 000 willingness to pay.

A total of 9 (21.9%) studies looking into the cost-effectiveness of neuropsychological or cognitive interventions were identified. These interventions consisted of behavioral treatments (n = 1), group memory programs (n = 1), problem-solving therapy (n = 3), and mediated therapy (n = 4).

A total of 6 studies reported CEA and 3 reported CUA. Eight studies were conducted in high-income countries and 1 study in a middle-income country. Three studies focused on patients with TBI, and 5 studies focused solely on stroke patients. Five studies were RCTs, 3 were model studies, and 1 was a non-RCT study. One behavioral therapy study[46] resulted in a decrease of 6 on the SADQH-21 indicating an improvement in mood, whereas the control group increased by 0.7. This difference was statistically significant (95% CI 2.45-11.61, $P = .003$). Overall, there were costs of £1541.70 in the control group compared with £1388.90 in the intervention group—a saving of £152.80; nevertheless, these results were not statistically significant ($P = .26$). One memory rehabilitation study[47] generated less quality-adjusted life-years (QALYs), with 0.011 (95% CI −0.031 to 0.01) fewer QALYs generated than usual care, but this was not statistically significant ($P = .44$). The intervention reported cost savings of £27 per patient; nevertheless, these results were also not significant (95% CI −455.13 to 401.34, $P = .91$). A total of 3 meditated therapy interventions[48-50] concluded that meditated therapy was more effective and cheaper than usual care with incremental cost-effectiveness ratio (ICER) values ranging from £192 to £12 214 (costs converted to price year 2020 sterling prices).

A total of 10 studies (24%) assessed the cost-effectiveness of allied health professional interventions. Of these, 6 were classified as occupational therapy interventions, 3 were physical activity related interventions, and 1 was a speech and language therapy intervention. Nine studies reported CEA and only 1 study reported CUA. All 10 studies were conducted in high-income countries. Two studies focused on patients with TBI, and 8 studies focused solely on stroke patients. Seven studies were RCTs, 2 were model studies, and 1 was a cohort study. Three of the occupational therapy interventions[51-53] reported cost savings ranging from £3987 to £5922 (costs converted to price year 2020 sterling prices). For instance, Mortimer et al[51] found that structured activity of daily living (ADL) retraining significantly increased functional independence (mean difference 5.22, Standard error 1.4, 95% CI 1.8-8.7) compared with treatment as usual (TAU). ADL retraining was also found to be cost saving compared with TAU, with a mean difference of −$7762 (95% CI −$8105 to −$7419). The results indicated that structured ADL retraining dominates (less costly but no less effective) than TAU. Another study by Patel et al[53] found that patients in the intervention group stayed in hospital less long (mean difference −12.4 days, 95% CI −19.5 to −5.6, $P < .001$). The

Table 1. Characteristics of included studies (N = 41).

| Characteristics | Included studies n (%) | References |
|---|---|---|
| Country type: | | |
| - High-income countries | 37 (90.2) | 30-33,35-46,48,50-60,69 |
| - Low- and middle-income countries | 4 (9.8) | 29,34,49,69 |
| Type of economic evaluation: | | |
| - Cost-utility analysis | 10 (24.4) | 30,32,40,47,50,58 |
| - Cost-effectiveness analysis | 29 (70.7) | 29,31,33-39,41-46,48,49,51-56,59-69 |
| - Cost analysis | 2 (4.8) | 57,60 |
| Perspective of cost: | | |
| - Healthcare system | 18 (43.9) | 31,35,36,38,41,43,46,48,49,51,54,55,57,60,61,63,65,69 |
| - Insurance company | 1 (2.4) | 30 |
| - Healthcare system and Societal | 10 (24.4) | 33,37,42,47,50,53,56,58,62,64 |
| - Societal | 9 (21.9) | 29,32,34,40,44,45,52,67,68 |
| - Not stated | 3 (7.3) | 39,59,66 |
| Time horizon for evaluation: | | |
| - < 1 year | 15 (36.6) | 29,34,36,41,43,46,47,55-57,60,61,64,69 |
| - 1-5 years | 19 (46.3) | 31,33,35,37,38,40,42,44,45,50,52-54,58,59,62,63,67,68 |
| - 10 years | 1 (2.4) | 39 |
| - Lifetime | 3 (7.3) | 30,32,49 |
| - Not stated | 3 (7.3) | 48,65,66 |
| Type of study: | | |
| - RCT | 24 (58.5) | 29,30,33,34,37,38,40,42,44,46-48,51-61,64,65,68,69 |
| - Cohort study | 3 (7.3) | 30,34,42 |
| - Non-RCT | 6 (14.6) | 36,41,43,45,66 |
| - Simulation model | 8 (19.5) | 31,32,35,49,50,54,55,63 |
| Target population: | | |
| - People with a diagnosis of ABI | 1 (2.4) | 45 |
| - People with a diagnosis of TBI only | 8 (19.5) | 31,41,42,47,51,62,63,66 |
| - People with a diagnosis of stroke only | 32 (78.0) | 29,30,32-40,43,44,46,48-50,52-61,63-65,67-69 |
| Interventions assessed: | | |
| - Home rehabilitation or early supported discharge (ESD) | 5 (12.2) | 57-60,69 |
| - Multidisciplinary rehabilitation | 17 (41.5) | 29-38,40-45,54 |
| - Neuropsychological or cognitive | 9 (21.9) | 46-50,63,67,68 |
| - Allied health professional | 10 (24.4) | 51-56,61,62,64,65 |
| Funding source: | | |
| - Nongovernmental | 20 (48.8) | 29,30,33,34,36-38,40,42,44-47,52,54-56,62,65,69 |
| - Governmental | 6 (14.6) | 31,53,58,59,61,63 |
| - Industry funding | 5 (12.2) | 32,35,50,67,68 |

ABI indicates acquired brain injury; ESD, early supported discharge; RCT, randomized controlled trial; TBI, traumatic brain injury.

total health and social care costs over 1 year for patients whose caregivers received training were significantly lower, with a mean difference of £4043 (95% CI £6544-£1595, $P < .0001$). Two of the physical activity interventions studies[54,55] were reported to be cost-effective, with ICER estimates ranging from £2598 to £9457. One speech and therapy intervention by Bowen et al[56] was reported not to be cost-effective. The study reported that the intervention resulted in a slight improvement of 0.01 (95% CI –0.19 to 0.69) points on the primary outcome therapy outcome measure activity subscale; nevertheless, the intervention costs on average £110 more per person than UC treatment. Sensitivity analysis indicated a 50% probability of the intervention being cost-effective at the threshold of £25 000 to gain a one-point increase in utility.

A total of 5 studies assessed the health and economic benefits of home rehabilitation (n = 2) or ESD interventions (n = 3). All 5 of these studies were RCTs, which lasted <13 months. A total of 3 of these studies reported CEA and 2 studies reported CA. A total of 4 studies were conducted in high-income countries, whereas only 1

**Table 2.** Summary of included studies.

| First author, years (country) | Target population group (total sample size) | Description of intervention (group sample size) | Comparator (control sample size) | Perspective and resources measured | | | | | | | Drummond score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Societal | | | | | | | |
| | | | | Health and social | | | | | Productivity | Informal care | |
| | | | | Healthcare | | | | Social care | | | |
| | | | | Intervention | Inpatient | Outpatient | Community | | | | |
| Home rehabilitation or ESD | | | | | | | | | | | |
| Anderson et al[57] (AU) | Patients with acute stroke who required rehabilitation (n = 86) | Early hospital discharge and home-based rehabilitation (n = 42) | Conventional hospital care (n = 44) | ✔ | - | ✔ | ✔ | ✔ | - | - | 3B |
| Mcnamee et al[58] (UK) | Patients admitted to either Freeman Hospital, Newcastle General Hospital, or Royal Victoria Infirmary in Newcastle upon Tyne with acute stroke (n = 92) | Early supported discharge (ESD) (n = 46) | Conventional hospital care (n = 46) | - | ✔ | ✔ | - | - | - | - | 4 |
| Rasmussen et al[59] (DK) | Women with focal neurological deficits hospitalized in a stroke unit for > 3 days and in need of rehabilitation (n = 71) | Home-based rehabilitation (n = 38) | TAU (n = 31) | ✔ | ✔ | ✔ | - | ✔ | - | - | 4 |
| Sritipsukho et al[69] (TH) | Patients with stroke because of middle cerebral artery infarction (n = 58) | Home rehabilitation program (n = 28) | UC (n = 30) | ✔ | - | - | ✔ | ✔ | - | - | 4 |
| Teng et al[60] (CA) | Persistent motor deficits after stroke who had caregivers willing and able to provide live-in care for the subject over a 4-week period after discharge from hospital (n = 114) | Early supported discharge (ESD) (n = 58) | UC (n = 56) | ✔ | ✔ | - | ✔ | ✔ | - | ✔ | 3B |
| Multidisciplinary rehabilitation | | | | | | | | | | | |
| Abdul Aziz et al[29] (MY) | Poststroke patients either discharged from hospital or undergoing treatment at public health centers, aged 18 years and older, any type of stroke (n = 151) | Integrated care pathway for poststroke patients (iCaPPS) (n = 86) | Conventional care (n = 65) | ✔ | - | - | ✔ | ✔ | ✔ | ✔ | 4 |
| Allen et al[30] (CA) | Adult stroke survivors who are unable to access traditional outpatient rehabilitation services (n = 164) | Community Stroke Rehabilitation Teams (CSRT) (n = 164) | UC (n = not stated) | ✔ | ✔ | ✔ | ✔ | ✔ | - | - | 4 |
| Andelic et al[31] (NO) | Patients with severe TBIs who survived 5 years after injury (n = 59) | Continuous chain rehabilitation (n = 30) | Broken chain rehabilitation (n = 29) | ✔ | ✔ | ✔ | - | - | - | - | 4 |

*continued on next page*

**Table 2.** Continued

| First author, years (country) | Target population group (total sample size) | Description of intervention (group sample size) | Comparator (control sample size) | Perspective and resources measured | | | | | | | Drummond score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Societal | | | | | | | |
| | | | | Health and social | | | | | Productivity | Informal care | |
| | | | | Healthcare | | | | Social care | | | |
| | | | | Intervention | Inpatient | Outpatient | Community | | | | |
| Chen et al[39] (TW) | Stroke patients (n = 14 544) | Transfer to rehabilitation ward (TR) (n = 9696) | No rehabilitation (n = 4848) | ✔ | ✔ | - | ✔ | - | - | - | **4** |
| Demaerschalk et al[32] (US) | Stroke survivors (n = not stated) | Telestroke network (n = not stated) | No network (n = not stated) | ✔ | ✔ | ✔ | - | ✔ | - | ✔ | **4** |
| Forster et al[33] (UK) | Confirmed diagnosis of stroke, medically stable, likely to return home with residual disability at the time of discharge, and had a caregiver available (n = 928) | London Stroke Carers Training Course (n = 450) | UC (n = 478) | ✔ | - | ✔ | ✔ | - | | | **4** |
| Gao et al[40] (AU, NZ, UK, SG, MY) | Patients (aged 18 years) with ischemic or hemorrhagic stroke (n = 2104) | Rehabilitation within 24 hours of stroke onset (AVERT) (n = 1054) | UC (n = 1050) | ✔ | - | ✔ | ✔ | ✔ | ✔ | | **4** |
| Grieve et al[41] (UK) | All adult patients admitted to participating critical care units with a confirmed TBI and a last presedation Glasgow coma scale (GCS) of 3-14 were included (n = 847) | Early transfer to neuroscience center (n = 584) | No or late transfer to center (n = 263) | ✔ | ✔ | - | - | - | - | - | **4** |
| Khiaocharoen et al[34] (TH) | Adult patients older than 17 years with a first episode of stroke (n = 207) | Rehabilitation service (SNAP) (n = 117) | Unexposed group (n = 90) | ✔ | ✔ | - | ✔ | ✔ | - | - | **4** |
| Radford et al[42] (UK) | Adults with TBI admitted for > 48 hours and working or studying before injury (n = 78) | Early specialist vocational rehabilitation (n = 39) | UC (n = 39) | ✔ | ✔ | ✔ | - | ✔ | ✔ | ✔ | **4** |
| Rodgers et al[37] (UK) | Adults with a new stroke (n = 573) | Extended stroke rehabilitation service (EXTRAS) (n = 285) | UC (n = 288) | ✔ | - | ✔ | ✔ | ✔ | - | - | **4** |
| Shaw et al[38] (UK) | Adults aged 18+ years with confirmed diagnosis of new stroke (n = 573) | Extended stroke rehabilitation service EXTRA (n = 285) | UC (n = 288) | ✔ | - | ✔ | ✔ | ✔ | - | - | **4** |
| Switzer et al[35] (US) | Stroke (n = 400) | Telestroke network (n = 282) | No network (n = 118) | ✔ | ✔ | - | ✔ | ✔ | - | - | **4** |
| Tam et al[43] (CA) | Stroke (n = not stated) | Fast-track stroke rehabilitation program (FT) (n = 100) | UC (n = not stated) | ✔ | - | ✔ | ✔ | ✔ | - | - | **4** |

*continued on next page*

**Table 2.** Continued

| First author, years (country) | Target population group (total sample size) | Description of intervention (group sample size) | Comparator (control sample size) | Perspective and resources measured | | | | | | | Drummond score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Societal | | | | | | | |
| | | | | Health and social | | | | | Productivity | Informal care | |
| | | | | Healthcare | | | | Social care | | | |
| | | | | Intervention | Inpatient | Outpatient | Community | | | | |
| Tay-Teo et al[44] (AU) | Hospitalized, ischemic, or hemorrhagic strokes, recruited within 24 hours of stroke onset (n = 71) | Very early mobilization in addition to standard care (VEM) (n = 38) | Standard care alone (n = 33) | ✔ | - | ✔ | ✔ | ✔ | ✔ | ✔ | 4 |
| van Exel et al[36] (NL) | Stroke patients admitted to hospital (n = 598) | Care through integrated stroke services (n = 411) | Conventional stroke care (n = 187) | ✔ | - | ✔ | ✔ | - | - | - | 4 |
| Wijnen et al[45] (NL) | Multitrauma patients in hospitals, severity scale score ≥ 16, complex multiple injuries in several extremities, or complex pelvic and acetabulum fractures (n = 132) | Fast track (n = 65) | Conventional multitrauma care (n = 67) | ✔ | ✔ | - | ✔ | - | ✔ | - | 4 |
| Neuropsychological or cognitive intervention | | | | | | | | | | | |
| Carpino et al[48] (IT) | First stroke, 18+ years, sufficient cognitive and communication for rehabilitation sessions, and do not have cardiac, psychological, or orthopedic problems (n = 1064) | Robot-mediated therapy plus additional manual therapy (n = n/a) | Conventional therapy (n = n/a) | ✔ | - | ✔ | - | ✔ | - | - | 4 |
| das Nair et al[47] (UK) | People with memory problems after TBI, aged 18-69 years travel to group sessions, communicate in English, and give consent (n = 328) | Group-based memory rehabilitation (n = 171) | UC (n = 157) | ✔ | - | ✔ | - | ✔ | - | - | 4 |
| Geng et al[49] (CN) | All eligible patients were aged between 18 and 80 years, in the poststroke stage and relatively serious (n = 2000) | Bobath rehabilitation (n = 1000) | Usual rehabilitation (n = 1000) | ✔ | - | ✔ | - | - | - | - | 4 |
| Humphreys et al[46] (UK) | Low mood on either the visual analog mood scale sad item (> 50) or stroke aphasic depression 1uestionnaire hospital version 21 (SADQH21) (> 6) (n = 87) | Behavioral therapy (BT) (n = 42) | TAU (n = 45) | ✔ | - | ✔ | - | ✔ | - | - | 4 |

*continued on next page*

**Table 2.** Continued

| First author, years (country) | Target population group (total sample size) | Description of intervention (group sample size) | Comparator (control sample size) | Perspective and resources measured | | | | | | | Drummond score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Societal | | | | | | | |
| | | | | Health and social | | | | | Productivity | Informal care | |
| | | | | Healthcare | | | | Social care | | | |
| | | | | Intervention | Inpatient | Outpatient | Community | | | | |
| Lazzaro et al[50] (IT) | Adult stroke survivors (n = not stated) | Rehabilitation + BoNT-A (n = not stated) | Rehabilitation (n = not stated) | ✔ | ✔ | - | ✔ | ✔ | ✔ | ✔ | 4 |
| Richardson et al[63] (US) | Military service members with TBI (n = 356) | Problem-solving therapy (PST) (n = 178) | Education only (EO) (n = 178) | ✔ | - | - | - | ✔ | - | - | 4 |
| Schoenberg et al[66] (US) | Participants who had sustained moderate to severe closed head TBIs and were residing in the state of Oklahoma (n = 39) | Group computer-based teletherapy services (n = 19) | Speech and language (n = 20) | ✔ | - | - | ✔ | ✔ | - | - | 4 |
| van Eeden et al[67] (NL) | Stroke patients (aged 18+ years) with signs of depression (Hospital Anxiety and Depression Scale [HADS]—subscale depression > 7) (n = 61) | Goal setting and goal attainment (augmented CBT) (n = 31) | Cognitive training program (n = 30) | ✔ | - | - | ✔ | ✔ | ✔ | - | 4 |
| van Mastrigt et al[68] (NL) | Stroke patients (18+ years) who suffered a first or recurrent symptomatic stroke (ie, ischemic or intracerebral hemorrhagic) (n = 113) | Self-management using proactive coping action planning (n = 58) | Education-based intervention (n = 55) | ✔ | - | - | - | - | ✔ | ✔ | 4 |
| Allied health professional interventions (eg, occupational, physical, and speech therapy) | | | | | | | | | | | |
| Adie et al[61] (UK) | Participants aged 24-90 years with arm weakness after a stroke within the previous 6 months (n = 235) | WiiTM console (n = 117) | Arm exercises at home (n = 118) | ✔ | - | - | ✔ | - | - | - | 4 |
| Bowen et al[56] (UK) | Adults with aphasia or dysarthria admitted to hospital with stroke (n = 170) | Speech and language therapy intervention (n = 85) | Attention control (n = 85) | ✔ | ✔ | ✔ | ✔ | - | - | ✔ | 4 |
| Chan[54] (CA) | Stroke patients who require PT rehabilitation (n = 3417) | Higher-intensity physiotherapy (HT) (n = missing) | Physiotherapy (n = missing) | ✔ | - | - | ✔ | - | - | - | 4 |
| Collins et al[55] (UK) | Stroke survivors that can walk independently and had capacity to consent to taking part in the classes. Carers were not involved in the intervention (n = 66). | Fitness program (n = 32) | Relaxation group (n = 34) | ✔ | - | ✔ | - | - | - | - | 4 |

*continued on next page*

**Table 2.** Continued

| First author, years (country) | Target population group (total sample size) | Description of intervention (group sample size) | Comparator (control sample size) | Perspective and resources measured: Societal: Health and social: Healthcare: Intervention | Inpatient | Outpatient | Community | Social care | Productivity | Informal care | Drummond score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mortimer et al[51] (AU) | Patients with a severe TBI admitted to an inpatient rehabilitation center (n = 104) | Structured activities of daily living (ADLs) retraining (n = 49) | TAU (n = 55) | ✔ | - | ✔ | - | - | - | - | 4 |
| Nagayama et al[52] (JP) | Stroke (cerebral infarct or intracerebral hemorrhage), within 30 days, age ≥ 40 and no major cognitive deficits (MMSE ≥ 24) aphasia or depression as an obstacle to daily living (n = 48) | Aid for Decision Making in Occupation Choice (n = 24) | Impairment-based approach (n = 24) | ✔ | - | ✔ | - | ✔ | - | - | 4 |
| Patel et al[53] (UK) | Stroke patients and their care givers (n = 300) | Caregiver training in basic nursing (n = 151) | No training (n = 149) | ✔ | - | - | ✔ | - | - | ✔ | 4 |
| Radford et al[62] (UK) | Patients admitted to Nottingham hospitals with a diagnosis of TBI and who were aged older than 16 years and in paid or voluntary work or education at the time of injury (n = 94) | TBI specialist Vocational Rehabilitation (n = 40) | UC (n = 54) | ✔ | ✔ | ✔ | ✔ | - | ✔ | ✔ | 4 |
| Roderick et al[64] (UK) | Stroke patients aged 55+ years who required rehabilitation after hospital discharge or after referral to geriatricians from the community (n = 112) | Domiciliary rehabilitation service (n = 54) | Day hospital care (n = 58) | ✔ | ✔ | - | ✔ | ✔ | - | - | 4 |
| Sampson et al[65] (UK) | adult stroke patients (n = 65) | Home assessment visit (n = 37) | Home assessment interview (n = 28) | ✔ | - | ✔ | - | ✔ | - | - | 4 |

AU indicates Australia; CA, Canada; CN, China; DK, Denmark; ESD, early supported discharge; IT, Italy; JP, Japan; MY, Malaysia; NL, The Netherlands; NO, Norway; NZ, New Zealand; SG, Singapore; TAU, treatment as usual; TBI, traumatic brain injury; TH, Thailand; TW, Taiwan; UC, usual care; UK, United Kingdom; US, United States.

was conducted in a low-income country. All 5 studies targeted population group of stroke survivors. The 2 main outcome measures reported in all studies included cost savings and reduction in hospital stay. A total of 4 studies[57-60] reported that ESD was a cost-effective alternative to usual care, with cost savings ranging from £142 to £1760 (costs converted to price year 2020 sterling prices). For instance, in a study by Teng et al,[60] which examined the caregiver cost of providing stroke patients with received ESD at home compared with usual care, reported that the total cost of home care was lower at $7784 (SD 3858) than $11 065 (SD 7504) for the usual care group ($P$ = .018). The average cost of providing a 4-week intervention was $943 per person. Physical health was also higher for those in the intervention group 45.9 (SD 10.1) than usual care 37.9 (SD 10.6) (mean difference 5, $P$ = .018) and that caregiver burden was lower by 5.3 points (standard error 2.3, $P$ = .02). The study concluded that, for persons recovering from stroke and their families, ESD provides a cost-effective alternative to usual care.

## Discussion

This systematic review highlights recent evidence on health economic evaluations of nonpharmacological interventions for individuals living with an ABI. To the best of our knowledge, this is the first systematic review focusing on nonpharmacological interventions directly delivered to patients with ABI or informal caregivers. The strength of this review includes a registered peer-reviewed protocol and a comprehensive search strategy in multiple databases. Additionally, the search terms were certified by a specialist librarian with expert knowledge in systematic reviews. Another strength to this study is that it offers costs converted to present day values (price year: 2020) and prices in a single currency (US dollars) using consumer price index and purchasing power parity, which allows easy comparison purpose between studies.

### *Limitations*

Even though a comprehensive literature search based on broad search terms was conducted, some articles meeting the search criteria might not have been identified. Moreover, articles written in languages other than English were excluded from the review, which might have led to language and publication bias. The weak descriptions of the interventions or comparator in most studies was a barrier to determining the cost-effectiveness of nonpharmacological interventions. Additionally, high levels of heterogeneity between studies make it difficult to identify the cost-effectiveness of rehabilitation interventions.

### *Implications for Future Research*

A substantial lack of economic evidence on nonpharmacological interventions for individuals with an ABI has been conducted in low- to middle-income countries. This is surprising given that highest incidence rates of stroke and TBI were observed in East Asia, especially in China, followed by Eastern Europe.[2,70] Our systematic review identified no economic evaluation studies that had been conducted in Eastern Europe and only 1 study in China that conducted an economic evaluation. A recommendation from this review would be that more research be conducted in low- to middle-income countries, which have the highest incidence rates of ABI.

Additionally, although this review included studies from several different countries, each of these countries has a different threshold, and although 1 country may determine a study to be cost-effective, it may be the case that if the study was to be replicated in another country, depending on policy and budget constraints of that country, it may not be considered cost-effective. In Ireland, guidelines for economic evaluation provided by Health Information and Quality Authority state that a threshold guidance between €20 000 and €45 000/QALY be used.[71] Under this assumption, any intervention that had an ICER higher than €45 000 per QALY would be less likely to be reimbursed based on it representing value for money. In contrast, the National Institute for Health and Care Excellence in the United Kingdom suggest a threshold of £20 000 to £30 000 per QALY.[72] Despite this guidance, interventions with ICERs above £30 000 or £50 000 are often accepted,[73,74] which indicates that cost-effectiveness is only one criterion that should be considered when making informed decisions. Other countries (including Canada, Brazil, Australia, and Sweden) do not specify an explicit threshold.[75] These variations in guidelines make it difficult to determine which interventions would be most suitable for ABI rehabilitation and will ultimately vary depending on each countries resources and budget constraints.[75] Therefore, we would recommend that future research should be conducted to determine what the optimal threshold levels should be for each country.

A high percentage of studies primarily only discussed costs from a healthcare perspective; other aspects (ie, beyond just a health budgetary perspective) that also need to be considered, including what wider society or individuals would be willing to pay; social and legal aspects; or ethical issues associated with each intervention. A recommendation of this review would be for future studies to include both a healthcare and societal perspective (ie, productivity and informal care costs), when conducting economic evaluations in this field.

All these other aspects are important to consider when formulating public policy.

Despite its importance, the prevalence of diseases such as stroke, TBI, or ABI is limited.[2,70] Economic evaluation studies have predominately focused solely on stroke research (n = 32), followed by TBI (n = 8), with only 1 study having conducted an economic evaluation on individuals with a diagnosis of ABI (n = 1). We would recommend that future studies should not only examine stroke populations but also consider other brain injury populations such as those with a TBI or other type of ABI (brain tumor, encephalitis).

A large number of individuals with an ABI are supported by family members, because they need continuous support and assistance in ADLs.[76] The findings from our review found that <25% of studies included both a healthcare and societal perspective in their economic analysis. Most studies (43.9%) focused solely on the healthcare costs associated with ABI. To determine the economic burden of ABI, future economic evaluation studies should also consider the indirect costs of stroke such as productivity loss and informal caregiving costs.

Additionally, individuals who have an ABI disorder are likely to require lifetime rehabilitation treatment; it is alarming that <3% of economic evaluations considered a lifetime time horizon in their analysis. Indeed, with approximately 83% of economic evaluation research conducted to date having a time horizon of <5 years. Taking into consideration, both the social costs associated with having an ABI and examining the lifetime horizons costs associated with having an ABI would be useful to decision makers and researchers for developing strategies for ABI prevention, treatment, and rehabilitation.

## Conclusions

This review provides evidence on economic aspects of nonpharmacological interventions in the rehabilitation field of ABI. Health economic evaluations suggest that ABI rehabilitation interventions improve health compared with usual care, and some evidence does suggest that they also save money; nevertheless, the evidence to date is scarce, and more research is urgently needed to examine the cost-effectiveness of such rehabilitation interventions. Unfortunately, even in the year 2022, research in the field of ABI remains severely underfunded. For instance, in the United Kingdom, stroke care has received considerably less research investment compared with other health conditions.[77] For every £10 allocated to health and social care research, cancer receives £1.08 in research funding, chronic heart disease receives £0.65, and stroke care receives only £0.19.[77] It is hoped that this review highlights the need for more economic evidence-based research in this field.

## Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2022.03.014.

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## REFERENCES

1. Maas AI, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol*. 2017;16(12):987–1048.
2. Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(5):439–458.
3. Patel AP, Fisher JL, Nichols E, Abd-Allah F, Abdela J, Abdelalim A. Global, regional, and national burden of brain and other CNS cancer, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(4):376–393.
4. Menon DK, Bryant C. Time for change in acquired brain injury. *Lancet Neurol*. 2019;18(1):28.
5. Chen A, Bushmeneva K, Zagorski B, Colantonio A, Parsons D, Wodchis WP. Direct cost associated with acquired brain injury in Ontario. *BMC Neurol*. 2012;12(1):76.
6. Alali AS, Burton K, Fowler RA, et al. Economic evaluations in the diagnosis and management of traumatic brain injury: a systematic review and analysis of quality. *Value Health*. 2015;18(5):721–734.
7. Ezekiel L, Field L, Collett J, Dawes H, Boulton M. Experiences of fatigue in daily life of people with acquired brain injury: a qualitative study. *Disabil Rehabil*. 2021;43(20):2866–2874.
8. Olofsson A, Larsson Lund M, Nyman A. Everyday activities outside the home are a struggle: narratives from two persons with acquired brain injury. *Scand J Occup Ther*. 2020;27(3):194–203.
9. Cattelani R, Zettin M, Zoccolotti P. Rehabilitation treatments for adults with behavioral and psychosocial disorders following acquired brain injury: A systematic review. *Neuropsychol Rev*. 2010;20(1):52–85.
10. De Luca R, Calabrò RS, Bramanti P. Cognitive rehabilitation after severe acquired brain injury: current evidence and future directions. *Neuropsychol Rehabil*. 2018;28(6):879–898.
11. Peppel LD, Ribbers GM, Heijenbrok-Kal MH. Pharmacological and non-pharmacological interventions for depression after moderate-to-severe traumatic brain injury: A systematic review and meta-analysis. *J Neurotrauma*. 2020;37(14):1587–1596.
12. Elbaum J. Acquired brain injury and the family: challenges and interventions. In: *Acquired Brain Injury*. Berlin, Germany: Springer; 2019:335–347.
13. Laatsch L, Dodd J, Brown T, et al. Evidence-based systematic review of cognitive rehabilitation, emotional, and family treatment studies for children with acquired brain injury literature: from 2006 to 2017. *Neuropsychol Rehabil*. 2020;30(1):130–161.
14. Turner-Stokes L. The evidence for the cost-effectiveness of rehabilitation following acquired brain injury. *Clin Med*. 2004;4(1):10.
15. Beecham J, Perkins M, Snell T, Knapp M. Treatment paths and costs for young adults with acquired brain injury in the United Kingdom. *Brain Inj*. 2009;23(1):30–38.
16. Adam T, Murray C. Making choices in health: WHO guide to cost-effectiveness analysis. World Health Organization. https://www.who.int/choice/publications/p_2003_generalised_cea.pdf. Accessed January 2, 2022.
17. Rychetnik L, Frommer M, Hawe P, Shiell A. Criteria for evaluating evidence on public health interventions. *J Epidemiol Commun Health*. 2002;56(2):119–127.
18. Heslin M, Forster A, Healey A, Patel A. A systematic review of the economic evidence for interventions for family carers of stroke patients. *Clin Rehabil*. 2016;30(2):119–133.
19. Brady BK, McGahan L, Skidmore B. Systematic review of economic evidence on stroke rehabilitation services. *Int J Technol Assess Health Care*. 2005;21(1):15.
20. Boudour S, Barral M, Gory B, et al. A systematic review of economic evaluations on stent-retriever thrombectomy for acute ischemic stroke. *J Neurol*. 2018;265(7):1511–1520.
21. Sadeghi R, Treglia G. Systematic reviews, and meta-analyses of diagnostic studies: a practical guideline. *Clin Transl Imaging*. 2017;5(2):83–87.
22. Eileen Mitchell SS, Ahern E, Philips N, Mockler D, McGettrick G, Trépel D. Economic evaluations of acquired brain injury (ABI) rehabilitation interventions: a systematic review. PROSPERO. 2020 CRD42020187469. National Institute for Health Research. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020187469. Accessed January 2, 2022.
23. Mitchell E, Ahern E, Saha S, Trepel D. Neuropsychological rehabilitation interventions for people with an acquired brain injury. A protocol for a systematic review of economic evaluation. *HRB Open Res*. 2020;3:83.
24. Evers S, elle Goossens M, De Vet H, et al. Criteria list for assessment of methodological quality of economic evaluations: consensus on Health Economic Criteria The authors thank the following persons for their participation in the Delphi panel. *Int J Technol Assess Health Care*. 2016;21(2):240–245.
25. CPI OCED. Organization for Economic Co-operation and Development (OECD). https://www.oecd.org/economic-outlook/. Accessed February 2, 2022.
26. PPPPS, OECD. Organization for Economic Co-operation and Development (OECD). https://www.oecd.org/sdd/prices-ppp/. Accessed February 2, 2022.
27. Country WB. Groups L. Country classification. 2021. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed February 2, 2022.
28. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. *Cost Eff Resour Alloc*. 2013;11(1):6.
29. Abdul Aziz AF, Mohd Nordin NA, Muhd Nur A, Sulong S, Aljunid SM. The integrated care pathway for managing post stroke patients (iCaPPS((c))) in public primary care health centres in Malaysia: impact on quality adjusted life years (QALYs) and cost effectiveness analysis. *BMC Geriatr*. 2020;20(1):70.
30. Allen L, John-Baptiste A, Meyer M, et al. Assessing the impact of a home-based stroke rehabilitation programme: a cost-effectiveness study. *Disabil Rehabil*. 2019;41(17):2060–2065.
31. Andelic N, Ye J, Tornas S, et al. Cost-effectiveness analysis of an early-initiated, continuous chain of rehabilitation after severe traumatic brain injury. *J Neurotrauma*. 2014;31(14):1313–1320.
32. Demaerschalk BM, Switzer JA, Xie J, Fan L, Villa KF, Wu EQ. Cost utility of hub-and-spoke telestroke networks from societal perspective. *Am J Manag Care*. 2013;19(12):976–985.
33. Forster A, Dickerson J, Young J, et al. A cluster randomised controlled trial and economic evaluation of a structured training programme for caregivers of inpatients after stroke: the TRACS trial. *Health Technol Assess*. 2013;17(46):1–216.
34. Khiaocharoen O, Pannarunothai S, Riewpaiboon W, Ingsrisawang L, Teerawattananon Y. Economic evaluation of rehabilitation services for inpatients with stroke in Thailand: A prospective cohort study. *Value Health Reg Issues*. 2012;1(1):29–35.
35. Switzer JA, Demaerschalk BM, Xie J, Fan L, Villa KF, Wu EQ. Cost-effectiveness of hub-and-spoke telestroke networks for the management of acute ischemic stroke from the hospitals' perspectives. *Circ Cardiovasc Qual Outcomes*. 2013;6(1):18–26.

36. van Exel NJ, Koopmanschap MA, Scholte op Reimer W, Niessen LW, Huijsman R. Cost-effectiveness of integrated stroke services. *Q J M*. 2005;98(6):415–425.
37. Rodgers H, Howel D, Bhattarai N, et al. Evaluation of an extended stroke Rehabilitation Service (EXTRAS): a randomized controlled trial and economic analysis. *Stroke*. 2019;50(12):3561–3568.
38. Shaw L, Bhattarai N, Cant R, et al. An extended stroke rehabilitation service for people who have had a stroke: the EXTRAS RCT. *Health Technol Assess*. 2020;24(24):1–202.
39. Chen CM, Yang YH, Lee M, Chen KH, Huang SS. Economic evaluation of transferring first-stroke survivors to rehabilitation wards: A 10-year longitudinal, population-based study. *Top Stroke Rehabil*. 2020;27(1):8–14.
40. Gao L, Sheppard L, Wu O, et al. Economic evaluation of a phase III international randomised controlled trial of very early mobilisation after stroke (AVERT). *BMJ Open*. 2019;9(5):e026230.
41. Grieve R, Sadique Z, Gomes M, et al. An evaluation of the clinical and cost-effectiveness of alternative care locations for critically ill adult patients with acute traumatic brain injury. *Br J Neurosurg*. 2016;30(4):388–396.
42. Radford K, Sutton C, Sach T, et al. Early, specialist vocational rehabilitation to facilitate return to work after traumatic brain injury: the FRESH feasibility RCT. *Health Technol Assess*. 2018;22(33):1–124.
43. Tam A, Mac S, Isaranuwatchai W, Bayley M. Cost-effectiveness of a high-intensity rapid access outpatient stroke rehabilitation program. *Int J Rehabil Res*. 2019;42(1):56–62.
44. Tay-Teo K, Moodie M, Bernhardt J, et al. Economic evaluation alongside a phase II, multi-centre, randomised controlled trial of very early rehabilitation after stroke (AVERT). *Cerebrovasc Dis*. 2008;26(5):475–481.
45. Wijnen BFM, Hemmen B, Bouman AIE, et al. Cost-effectiveness of an integrated 'fast track' rehabilitation service for multi-trauma patients: A non-randomized clinical trial in The Netherlands. *PLoS One*. 2019;14(3):e0213980.
46. Humphreys I, Thomas S, Phillips C, Lincoln N. Cost analysis of the Communication and Low Mood (CALM) randomised trial of behavioural therapy for stroke patients with aphasia. *Clin Rehabil*. 2015;29(1):30–41.
47. das Nair R, Bradshaw LE, Day FE, et al. Clinical and cost effectiveness of memory rehabilitation following traumatic brain injury: a pragmatic cluster randomized controlled trial. *Clin Rehabil*. 2019;33(7):1171–1184.
48. Carpino G, Pezzola A, Urbano M, Guglielmelli E. Assessing effectiveness and costs in robot-mediated lower limbs rehabilitation: a meta-analysis and state of the art. *J Healthc Eng*. 2018;2018:7492024.
49. Geng R, Zhang J, Lv F, Sun Q. Cost-effectiveness analysis of reformative Bobath rehabilitation versus traditional rehabilitation in post-stroke syndrome. *Int J Clin Exp Med*. 2018;11(11):12246–12252.
50. Lazzaro C, Baricich A, Picelli A, Caglioni PM, Ratti M, Santamato A. AbobotulinumtoxinA and rehabilitation vs rehabilitation alone in post-stroke spasticity: a cost-utility analysis. *J Rehabil Med*. 2020;52(2):jrm00016.
51. Mortimer D, Trevena-Peters J, McKay A, Ponsford J. Economic evaluation of Activities of Daily Living retraining during posttraumatic amnesia for inpatient rehabilitation following severe traumatic brain injury. *Arch Phys Med Rehabil*. 2019;100(4):648–655.
52. Nagayama H, Tomori K, Ohno K, et al. Cost effectiveness of the occupation-based approach for subacute stroke patients: result of a randomized controlled trial. *Top Stroke Rehabil*. 2017;24(5):337–344.
53. Patel A, Knapp M, Evans A, Perez I, Kalra L. Training care givers of stroke patients: economic evaluation. *BMJ*. 2004;328(7448):1102.
54. Chan B. Effect of increased intensity of physiotherapy on patient outcomes after stroke: an economic literature review and cost-effectiveness analysis. *Ont Health Technol Assess S*. 2015;15(7):1–43.
55. Collins M, Clifton E, Wijck FV, Mead GE. Cost-effectiveness of physical fitness training for stroke survivors. *J R Coll Phys Edinb*. 2018;48(1):62–68.
56. Bowen A, Hesketh A, Patchick E, et al. Clinical effectiveness, cost-effectiveness, and service users' perceptions of early, well-resourced communication therapy following a stroke: a randomised controlled trial (the ACT NoW Study). *Health Technol Assess (Winchester, England)*. 2012;16(26):1–160.
57. Anderson C, Rubenach S, Mhurchu CN, Clark M, Spencer C, Winsor A. Home or hospital for stroke rehabilitation? results of a randomized controlled trial: I: health outcomes at 6 months. *Stroke*. 2000;31(5):1024–1031.
58. Mcnamee P, Christensen J, Soutter J, et al. Cost analysis of early supported hospital discharge for stroke. *Age Ageing*. 1998;27(3):345–351.
59. Rasmussen RS, Ostergaard A, Kjaer P, et al. Stroke rehabilitation at home before and after discharge reduced disability and improved quality of life: a randomised controlled trial. *Clin Rehabil*. 2016;30(3):225–236.
60. Teng J, Mayo NE, Latimer E, et al. Costs and caregiver consequences of early supported discharge for stroke patients. *Stroke*. 2003;34(2):528–536.
61. Adie K, Schofield C, Berrow M, et al. Does the use of Nintendo Wii Sports(TM) improve arm function? Trial of Wii(TM) in Stroke: a randomized controlled trial and economics analysis. *Clin Rehabil*. 2017;31(2):173–185.
62. Radford K, Phillips J, Drummond A, et al. Return to work after traumatic brain injury: cohort comparison and economic evaluation. *Brain Inj*. 2013;27(5):507–520.
63. Richardson JS, Guzauskas GF, Fann JR, et al. Economic evaluation of telephone-based concussion management for combat-related mild traumatic brain injury. *J Telemed Telecare*. 2018;24(4):282–289.
64. Roderick P, Low J, Day R, et al. Stroke rehabilitation after hospital discharge: a randomized trial comparing domiciliary and day-hospital care. *Age Ageing*. 2001;30(4):303–310.
65. Sampson C, James M, Whitehead P, Drummond A. An introduction to economic evaluation in occupational therapy: cost-effectiveness of pre-discharge home visits after stroke (HOVIS). *Br J Occup Ther*. 2014;77(7):330–335.
66. Schoenberg MR, Ruwe WD, Dawson K, McDonald NB, Houston B, Forducey PG. Comparison of functional outcomes and treatment cost between a computer-based cognitive rehabilitation teletherapy program and a face-to-face rehabilitation program. *Prof Psychol Res Pract*. 2008;39(2):169–175.
67. van Eeden M, Kootker JA, Evers SM, van Heugten CM, Geurts AC, van Mastrigt GA. An economic evaluation of an augmented cognitive behavioural intervention vs. computerized cognitive training for post-stroke depressive symptoms. *BMC Neurol*. 2015;15(1):266.
68. van Mastrigt G, van Eeden M, van Heugten CM, Tielemans N, Schepers VPM, Evers S. A trial-based economic evaluation of the Restore4Stroke self-management intervention compared to an education-based intervention for stroke patients and their partners. *BMC Health Serv Res*. 2020;20(1):294.
69. Sritipsukho P, Riewpaiboon A, Chaiyawat P, Kulkantrakorn K. Cost-effectiveness analysis of home rehabilitation programs for Thai stroke patients. *J Med Assoc Thai*. 2010;93(suppl 7):S262–S270.
70. James SL, Theadom A, Ellenbogen RG, Bannick MS, Montjoy-Venning W, Lucchesi LR. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(1):56–87.
71. O'Mahony JF, Coughlan D. The Irish cost-effectiveness threshold: does it support rational rationing or might it lead to unintended harm to Ireland's health system? *Pharmacoeconomics*. 2016;34(1):5–11.
72. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold. *Pharmacoeconomics*. 2008;26(9):733–744.
73. Schwarzer R, Rochau U, Saverno K, et al. Systematic overview of cost–effectiveness thresholds in ten countries across four continents. *J Comp Eff Res*. 2015;4(5):485–504.
74. Claxton K, Martin S, Soares M, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technol Assess (Winchester, England)*. 2015;19(14):1.
75. Woods B, Revill P, Sculpher M, Claxton K. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. *Value Health*. 2016;19(8):929–935.
76. McIntyre M, Ehrlich C, Kendall E. Informal care management after traumatic brain injury: perspectives on informal carer workload and capacity. *Disabil Rehabil*. 2020;42(6):754–762.
77. Luengo-Fernandez R, Leal J, Gray A. UK research spend in 2008 and 2012: comparing stroke, cancer, coronary heart disease and dementia. *BMJ Open*. 2015;5(4):e006648.