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Systematic Literature Review

Economic Evaluation of Stem Cell Therapies in Neurological Diseases: A Systematic Review

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ABSTRACT

Objectives: To examine economic evaluation studies of stem cell therapies (SCTs) in neurological disorders and to provide an overview of the quality of the economic evidence available on this topic. **Methods:** The review examined studies that performed an economic evaluation of the use of stem cells in adult patients with neurological diseases and that were published in English during the period 2007 to 2017. Data analyzed and reported included study population, disease indication, main analytical approaches for the economic analysis and perspective, key assumptions made or tested in sensitivity analyses, cost outcomes, estimates of incremental cost effectiveness, and approaches to quantifying decision uncertainty. **Results:** A total of three studies reporting on the findings of the economic evaluation of the use of SCT in stroke, Parkinson disease, and secondary progressive multiple sclerosis, respectively, were identified. All three studies conducted a cost-utility analysis using decision-analytic models and reported an incremental cost per quality-adjusted life-years gained (incremental cost-effectiveness ratio) versus standard care. These studies reported meaningful cost savings in stroke, Parkinson disease, and secondary progressive multiple sclerosis in the base-case scenarios. **Conclusions:** Despite significant progress in clinical research in the use of SCT in neurological diseases, economic evaluation of these therapies is still at a nascent stage. Given the early stage of research inputs (clinical and cost outcomes data) into the models per se, further research is urgently needed to enable meaningful assessment of the cost effectiveness of these advanced therapies and to ensure sustainable access for population groups most likely to benefit in clinical practice.

Keywords: economic evaluation, neurological disease, stem cells, stroke

Introduction

In recent decades, improved nutrition and health care have led to decreasing mortality across the entire spectrum of diseases. This has been associated with an increasing gap between life expectancy and healthy life expectancy. This gap has recently been reported to be more than 10 years, indicating increasing years of life with suboptimal health and disability [1]. Neurological diseases such as stroke [2], Parkinson disease (PD), Alzheimer disease, and progressive multiple sclerosis [3] have been increasingly contributing to this emerging pattern. Deterioration in quality of life associated with these conditions has either risen or stayed stable despite inroads made in terms of mortality. The situation is further worsened by the fact that, for most of these conditions, research into novel therapeutic options over the last few decades has met with multiple and costly failures [4].

In this context, regenerative medicine (cell/gene/bioengineering products) offers an exciting option for delivering a meaningful solution to the current unmet need from a patient and public health perspective [5]. Stem cell therapies (SCTs) potentially replace or regenerate diseased human cells, tissues, or organs to restore or establish normal function. Early-phase research in the use of SCT in stroke [6], Alzheimer disease [7], PD [8], and progressive multiple sclerosis [9] has indicated a potential for meaningful benefit. Despite the increased number of regulatory approvals for SCT in different countries, reimbursement and broad patient access remain challenges [5,10]. The personalized nature of their clinical application and assessment of health

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outcomes and measures of clinical effectiveness pose a challenge to an assessment of their value proposition [11].

The present global explosion in health care budgets has resulted in fiscal tightening of spending on research and clinical translation of innovative therapies [12]. In recent years, the evidence base has expanded to support the efficacy and safety of SCT in neurological diseases [6–9]. Generating economic evidence at an early stage can accelerate clinical translation by enabling strategic research and development decisions, preclinical market assessment, portfolio decisions, clinical trial design, and market access and pricing strategy arrangements [12–15]. Nevertheless, there has been no formative assessment of literature reporting economic outcomes in terms of cost effectiveness and value to patients or health care systems of SCT to date.

This systematic review presents an overview of the quantity and quality of economic evaluations of the use of SCT in neurological diseases. This is likely to become a critical determinant of successful translation of regenerative medicine as a viable clinical strategy.

Methods

Protocol and Registration

The protocol for the review was prepared and registered on PROSPERO (International Prospective Register of Systematic Reviews; Ref-CRD42017072937) [16].

Eligibility Criteria

All studies that performed an economic evaluation of the use of stem cells in adult patients with neurological diseases and that were published in English during the period 2007 to 2017, which reflects the period of maximum publications in the field of stem cell research, were eligible for inclusion. Although there were no restrictions on the types of study design eligible, studies of effectiveness that did not report costs and studies purely reporting the burden of disease or the cost of illness without including the intervention were excluded.

Search and Study Selection

Systematic searches were undertaken in MEDLINE, PubMed, CINAHL, Embase, PsycINFO, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, National Health Service Economic Evaluation Database, the Health Technology Assessment database, and the Cost-Effectiveness Analysis Registry. The reference lists of included studies were scanned for any additional studies. The database search used primary search terms on cell therapy, health economics, and neurological diseases (see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.07.878).

Data Extraction

The screening and data extraction for this review was conducted using the Covidence platform [17].

Two of the reviewers independently conducted screening against the inclusion/exclusion criteria and subsequent full-text review of all potentially relevant studies. Data extraction included study details (author, year of publication, country, and setting), study population, disease indication, main analytical approaches for the economic analysis and perspective, key assumptions made in the base case or tested in sensitivity analyses, costs, estimates of incremental cost-effectiveness, and approaches to quantifying decision uncertainty (e.g., deterministic and/or probabilistic sensitivity analysis). Any disagreements were resolved through consensus or by recourse to a third reviewer.

Quality Assessment

The quality was assessed using the revised checklist proposed in the International Society for Pharmacoeconomics and Outcomes Research Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Task Force Report [18]. One of the reviewers provided additional specific input on the quality assessment of analytical methods (item no. 17). Any disagreements were resolved through discussion or by recourse to a third reviewer. Each item was rated as "fully satisfied," "partially satisfied," or "not satisfied" or "not applicable."

Data Synthesis

A narrative synthesis, based on the preceding data extraction and quality appraisal, was undertaken. A meta-analysis was not feasible because of the low number of studies overall and the fact that eligible studies involved different diseases, SCT types, and input variables in the models. The costs were converted to a common currency (US dollars) and inflated to the price level of 2016 using the CCEMG-EPPI-Centre Cost Converter (version 1.4) for reporting [19].

Results

In total, 12,840 titles were identified in the preliminary search. Removal of duplicates resulted in 7116 potentially relevant articles. Of these, 6888 articles were excluded after screening of title and abstract, and 228 articles underwent a review of the full text. Of these articles, 225 were excluded for reasons provided in Figure 1. The remaining three studies were included in the review. Key descriptions of included studies are presented in Table 1. The quality assessment of these studies is presented in Table 2.

Study Characteristics: Disease Indication, Intervention, Design, Time Horizon, Discount Rate, and Perspective

The studies differed in terms of type of SCT used and neurological diseases studied: stroke [20], PD [21], and secondary progressive multiple sclerosis (SPMS) [22]. The PD study compared the use of embryonic neural stem cells with standard care. The study on SPMS looked at the use of hematopoietic stem cell transplantation (HSCT) versus mitoxantrone therapy. The stroke study model did not define the SCT type and compared assumed effect to existing standard care, on the basis of expert opinion.

The stroke and SPMS studies evaluated cost outcomes over a lifetime [20,22], whereas the PD study reported them over a 25-year horizon [21].

The SPMS study compared a patient cohort with SPMS who received HSCT to a matched comparator group receiving mitoxantrone as part of standard care [22]. The target population in the PD study included patients with motor impairment (Hoehn and Yahr [HY] stages III–IV) who received SCT [21]. The HY staging captures increasing severity (stage I [minimal impairment] to stage V [confinement to bed]) of progressive motor impairment in PD [23]. The data on the comparator population (standard care) were sourced from a clinical practice cohort [24]. The stroke study defined its target population as patient cohorts of age 55, 65, and 75 years with a modified Rankin Scale (mRS) score of 1 to 4 at discharge [20]. The mRS is commonly used to measure disability (0 indicates no disability and 6 is death) in patients with stroke [25]. The data for comparator population, that is, standard of care, were derived from a previous randomized multicenter study [26].

The stroke model allowed for subgroup analysis according to age at stroke onset, functional status at hospital discharge,

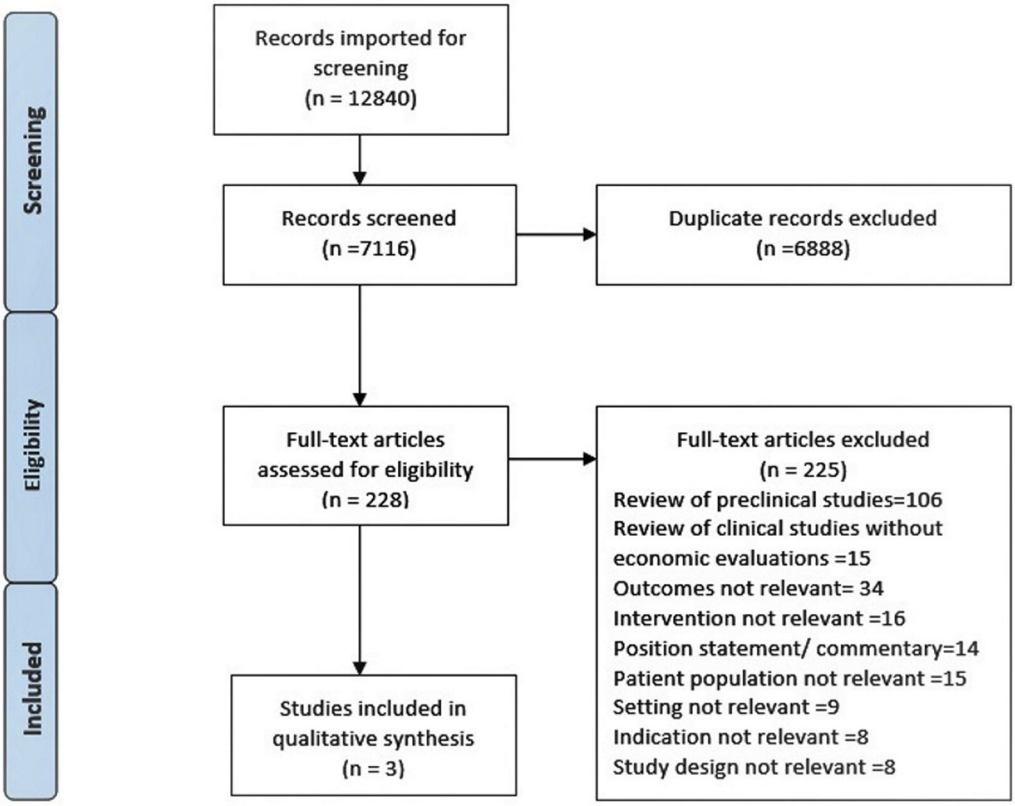

Fig. 1 – PRISMA flowchart [41]. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

assumed effectiveness of SCT, mode of stem cell administration, risk of recurrent stroke, or death caused by intervention [20]. The PD study evaluated subgroups according to age (<64 and ≥64 years) [21]. By comparison, the SPMS study did not report on any specified subgroups [22]. All three studies used discounting for future costs and benefits: the PD and stroke studies used a 3% discount rate for all calculations, as recommended in Sweden, whereas the SPMS study used 3.5%, in line with existing recommendations in the United Kingdom. The PD and SPMS studies examined the costs from a government perspective. The stroke study adopted a societal perspective.

Quality

All studies differed in the type of SCT used. The evidence from clinical studies to date does not indicate a significant difference in clinical effect of different cell types [27]. None of the studies has examined SCT type as a potential variable in the economic analysis model. The time horizon for model application was reported in all studies, but justification for the choice was missing. The selection of target and comparator populations is well described for all the studies. Only the SPMS study, however, reported matching the SCT cohort and comparator group on the basis of baseline diagnosis of SPMS and Expanded Disability Status Scale (EDSS) values [22]. The PD and stroke studies did not report whether the SCT and comparator had been matched. None of the studies explained in detail why the chosen perspective provides the most appropriate economic viewpoint of analysis. Two of three studies did not report on potential conflicts of interest.

Estimating Resources and Costs: Model-Based Evaluations and Currency

The PD study (Table 1) was limited to direct medical (hospital care, pharmaceuticals, and investigations) and direct nonmedical (transportations and home help) costs [21]. The cost data for management of PD, SCT transplantation, and associated complications were sourced from previous clinical studies. Calculations were made in euros (€) according to the price level of 2002.

The SPMS study included intervention costs (treatment costs for mitoxantrone and autologous HSCT and any related adverse events) and other costs (Table 1) associated with the management of multiple sclerosis [23]. Hospital resource use and pharmaceutical costs were calculated in pounds using the National Health Service and the British National Formulary reference costs for the year 2006 to 2007.

The stroke study included direct health care costs for initial and recurrent events (Table 1), sourced from a previous study. Long-term costs included social services and indirect costs owing to disability and productivity losses, sourced from a study on the cost of stroke in Sweden. Calculations were expressed in US dollars for the year 2009.

Quality

The PD study used resource costs from a previous study but provided limited details about where unit costs were derived from [28]. No opportunity costs were included. The stroke study drew from assumptions based on expert opinion and previously published literature but did not clearly describe where some unit costs were drawn from. Opportunity costs were not included. The SPMS study described the sources for cost estimations in detail. Nevertheless, indirect costs such as lost productivity and out-of-pocket expenses were excluded from the analysis.

Outcomes: Choice of Health Outcomes, Assumptions, and Valuation of Preference-Based Measures of Effectiveness

All the studies used quality-adjusted life-years (QALYs) as a health outcome. The PD model used effectiveness data from a clinical

Table 1 – Summary of included studies.

Study characteristic	Hjelmgren et al. [21]	Tappenden et al. [22]	Svensson et al. [20]
Disease indication	PD	SPMS	Stroke
Country	Sweden	United Kingdom	Sweden
Design	Markov state transition model	Markov state transition model	Decision tree model
Intervention	Embryonic neural stem cells	HSCT	Intracerebral stem cell implantation
Comparator	Standard pharmacological therapy	Mitoxantrone	Standard poststroke care
Base-case population	Idiopathic patients with PD (HY stage III–IV) aged ≤64 y	Patients with SPMS in two MS registries: the Lyon Clinique de Neurologie MS Registry and the EBMT MS registry	Cohort aged 55 y at stroke onset, with mRS 2 at hospital discharge, and an assumed increase in the probability to improve 1 mRS grade of 50% with SCT
Method	CUA	CUA	CUA/CBA
Time horizon	25 y	Lifetime	Lifetime
Perspective	Government (direct and nonmedical costs)	Government perspective (UK NHS and Personal Social Services)	Societal
Base-case scenario	Patients aged <64 years with early onset PD (HY stage III–IV) with an assumed	Patients with a baseline EDSS score ≥3 and ≤8; modeled with three scenarios with different interpretations of the disease progression	Patients aged 55 y at stroke onset, with mRS 2 at hospital discharge
Base-case assumptions	Initial progressive improvement during first 2 y, followed by a stationary period up to 5 y after transplantation, and return to preoperative rate of disease progression thereafter	Transitions between EDSS states may be progressive or regressive	Relative effectiveness of intracerebral SCT transplantation of 50% and no associated side effects
Discount (%)	3	3.5	3
Currency (y)	€ (2002)	£ (2006–2007)	US $ (2009)
Intervention costs (value in US $ inflated to 2016)	HY stage III: €156,467 (US $22,206) HY stage IV: €163,558 (US $23,212)	Scenario 1*: £131,666 (US $23,615) Scenario 2†: £124,262 (US $211,041) Scenario 3‡: £111,008 (US $188,531)	US $202,901 (US $224,918)
Comparator costs (value in US $ inflated to 2016)	HY stage III: €158,943 (US $22,557) HY stage IV: €186,279 (US $26,437)	Scenario 1*: £107,126 (US $181,938) Scenario 2†: £107,126 (US $181,938) Scenario 3‡: £107,126 (US $181,938)	US $221,956 (US $246,040)
QALYs gain	HY stage III: 0.873 HY stage IV: 1.133	Scenario 1*: −1.02 Scenario 2†: 0.23 Scenario 3‡: 1.40	1.34
ICER (value in US $ inflated to 2016)	HY stage III: cost-saving HY stage IV: cost-saving	Scenario 1*: dominated Scenario 2†: £74,210 (US $126,035) Scenario 3‡: £2,783 (US $4,726)	Cost-saving
Cost-effectiveness threshold (value in US $ inflated to 2016)	€38,000 (US $5,393) €70,000 (US $9,934)	£12,936 (US $21,358)	US $110,400 (US $122,379)
Sensitivity analysis	Univariate analysis: time horizon (10–20–30 y); discount rate (0%–5%); treatment efficacy (±50%); occurrence of complications (±100%); analytical perspective (direct medical costs only vs. including other direct costs); method of determining utilities	Univariate analysis: transplant-related mortality rate (0/1.3%); relative PFS hazard ratio between HSCT and mitoxantrone; tariff cost of HSCT (±25%), costs of managing MS (±25%); discount rate (0/3.5%) Scenario analysis: effectiveness duration	Univariate analysis: relative efficacy of SCT; mode of transplantation; age at stroke onset; annual risk of recurrent stroke; SCT procedure risk of death; intervention on mRS 3/4; extended leave period

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Table 1 – *continued*

Study characteristic	Hjelmgren et al. [21]	Tappenden et al. [22]	Svensson et al. [20]
Impact of variables on cost effectiveness	The results were sensitive for patients in HY stage III to changes in time horizon, discount rate, treatment effect, and health utility method, but were stable for patients in HY stage IV	Shorter treatment effect persistence resulted in HSCT not being cost-effective in optimistic scenario; decreased intervention cost and mortality risk associated with HSCT improved cost effectiveness	SCT remained cost-effective but societal value decreased—decreased QALY gain and increased incremental costs with decrease in relative efficacy, higher age at stroke onset; intervention in patients with higher disability (mRS 4)
Variable ranges included in analysis	No explanation provided	No explanation provided	Variable ranges based on expert opinion
Study findings	Long-term cost savings in most instances in early onset PD patients in HY stages III–IV	A potential to achieve a level of cost effectiveness that is acceptable to policymakers and health care purchasers, but is largely determined by the interpretation of available clinical effectiveness data and the duration over which such effects may be observed	A potential for long-term cost savings by reducing the disability after stroke; societal value up to US $166,500 (US $184,567), particularly in younger patients with stroke with moderate disability, with possible cost effectiveness estimated down to relative efficacy of 14%
Generalizability	Enables cost-effectiveness analysis based on real-world progression using a clinical surrogate end point (HY stages)	Focus on the potential cost effectiveness of autologous HSCT in the management of SPMS only	Enables CBA for patients with stroke under a wide range of assumptions
Limitations	Small number of patient- level data; clinical effectiveness data based on open-label transplantation trials	The absence of direct RCT evidence to input into the model	Effectiveness of SCT in humans was based on expert opinion; did not include differential costs on early vs. late administration poststroke; limited standard care data reflecting survival, treatment patterns, and transition probabilities for mRS

CBA, cost-benefit analysis; CUA, cost-utility analysis; EDSS, Expanded Disability Status Scale; HSCT, hematopoietic stem cell transplantation; HY, Hoehn and Yahr stages of PD; ICER, incremental cost-effectiveness ratio; mRS, modified Rankin Scale; MS, multiple sclerosis; NHS, National Health Service; PD, Parkinson disease; PFS, progression-free survival; QALY, quality-adjusted life-year; RCT, randomized controlled trial; SCT, stem cell therapy; SPMS, secondary progressive multiple sclerosis.
* Scenario 1: Strict 6-mo sustained progression from baseline EDSS.
† Scenario 2: Next-visit sustained progression from baseline EDSS.
‡ Strict 6-mo sustained progression from any EDSS.

practice [21] and an SCT study cohort [28] at their institution. Health state utilities were generated for every HY stage of PD, using the generic EuroQol five-dimensional questionnaire (EQ-5D), measured by the time trade-off method [29]. QALYs were obtained by multiplying the number of mortality-adjusted life-years spent in each HY stage with its health utility weight.

The stroke model used assumptions regarding effectiveness of stem cells on the basis of expert opinion. The change in function and quality of life after a stroke was classified into distinct health states in accordance with the different mRS scores. A previously published algorithm that translates the mRS into EQ-5D utility was used to generate QALYs for each mRS score [30].

The SPMS model sourced individual patient-level disease progression data from a real-world clinical practice registry (mitoxantrone) [31] and an HSCT patient registry and estimated relative effectiveness based on Kaplan-Meier progression-free survival curves [32]. Discrete health states, defined by the EDSS state (a measure of disability in SPMS), were associated with unique health-related quality of life. The time spent in each EDSS state weighted by its respective health-related quality-of-life level (from previous literature) provided an estimate of the number of QALYs gained in each treatment group.

Quality

All the studies reported QALYs as the health outcome. None of the studies, however, justified its choice in the study context. With respect to reporting study parameters, all the studies missed reporting variability around mean estimates of effectiveness.

Model-Based Economic Evaluations: Choice of Model and Analytical Method

All three studies conducted a cost-utility analysis of SCT versus standard care. In addition, the stroke study reported a cost-benefit analysis in terms of societal value expressed as the value of health benefits (QALYs × willingness to pay per QALY gain) less the incremental cost of SCT over standard care [20–22]. The stroke

Table 2 – Quality assessment of the included studies: CHEERS checklist.

Quality assessment items to report	Item no.	Study		
		Hjelmgren et al. [21]	Tappenden et al. [22]	Svensson et al. [20]
Title	1	PS	FS	FS
Abstract	2	PS	FS	PS
Background and objectives	3	FS	FS	FS
Target population	4	FS	FS	FS
Setting and location	5	FS	FS	FS
Study perspective	6	FS	FS	FS
Comparators	7	PS	FS	PS
Time horizon	8	FS	FS	FS
Discount rate	9	FS	FS	FS
Choice of health outcomes	10	PS	PS	PS
Measurement of effectiveness: single study–based estimates	11a	NA	NA	NA
Measurement of effectiveness: synthesis-based estimates	11b	FS	FS	FS
Measurement and valuation of preference-based outcomes	12	FS	PS	NS
Estimating resources and costs: single study–based economic evaluation	13a	NA	NA	NA
Estimating resources and costs: model-based economic evaluation	13b	PS	FS	PS
Currency, price, date, and conversion	14	FS	FS	FS
Choice of model	15	FS	FS	FS
Assumptions	16	FS	FS	FS
Analytical methods	17	FS	FS	FS
Study parameters	18	PS	PS	PS
Incremental costs and outcomes	19	FS	FS	FS
Characterizing uncertainty	20b	FS	FS	PS
Characterizing heterogeneity	21	FS	FS	PS
Study findings, limitations, generalizability, and current knowledge	22	PS	FS	FS
Source of funding	23	FS	FS	FS
Conflicts of interest	24	NS	FS	NS

CHEERS, Consolidated Health Economic Evaluation Reporting Standards; FS, fully satisfied; NA, not applicable; NS, not satisfied; PS, partially satisfied.

study used the decision tree model [20], but the PD and SPMS studies [21,22] used the Markov state transition model.

Quality

All the studies justified that their analytical method and choice of model, along with the input parameters used in the model, were appropriate, given the early stage of research with SCT. The models were explained using a schematic in the stroke and SPMS studies.

Incremental Costs and Outcomes

The PD study reported overall cost savings ($351.40 [HY stage III]; $3224.62 [HY stage IV]) and gains in QALYs (0.873 [HY stage III]; 1.133 [HY stage IV]) with the use of SCT in the base-case scenario: patients with early onset PD (HY stages III–IV) with an assumed initial improvement during the first 2 years, after a stationary period of up to 5 years after grafting, and return to preoperative rate of disease progression thereafter [21]. These were evaluated against the cost-per-QALY thresholds acceptable to UK ($5393) and Swedish ($9934) payers. This predicted that a price premium ($5109–$9083) was available for recovering investment on development.

The stroke study reported a QALY gain of 1.34. Although the SCT intervention increased costs by $70,960, these were offset by decrease in productivity losses to result in an overall saving of $21,122. SCT dominated standard care in terms of incremental cost-per-QALY gain in base-case population: patients were aged 55 years at stroke onset, had an mRS score of 2 at hospital discharge, and were given intracerebrally transplanted SCT with an assumed relative effectiveness of 50% and experiencing no side effects [20]. The study reported that the societal value of SCT in stroke was $184,567, assuming a Swedish willingness to pay for a QALY of $122,379. This represented a potential headroom of $21,122 per treatment for developers to realize a return on investment [20].

The SPMS study presented the central estimates of cost effectiveness for autologous HSCT versus mitoxantrone across three base-case scenarios incorporating different methods of measuring disease progression (EDSS) [22]. The study reported an incremental cost per QALY gained (incremental cost-effectiveness ratio) of $4726/QALY in the scenario in which disease progression was measured as EDSS progression sustained for 6 months from any EDSS [22]. Nevertheless, HSCT may be dominated (costlier and less effective) by mitoxantrone in the scenario in which confirmation of disease progression required sustained increase over 6 months since baseline. In the scenario requiring next-visit sustained progression from baseline, the incremental cost of $125,678/QALY gained was not cost-effective as per the UK threshold of $33,967 to $50,950/QALY [22].

Quality

All the studies reported on incremental costs and outcomes adequately in terms of costs per QALYs or incremental cost-effectiveness ratio as appropriate.

Characterizing Uncertainty

All three studies undertook univariate sensitivity analyses to test for the impact of changes in parameters included in the model on the study results. In addition, the SPMS study undertook a scenario analysis involving different durations of persistence of clinical benefit.

The PD study undertook a univariate sensitivity analysis to test whether changes in model specifications had an impact on the robustness of the results, focusing on the time horizon, discount rate, treatment efficacy, occurrence of complications, and changes in the analytical perspective (only direct medical costs vs. other direct costs as well). The outcome was varied from the EQ-5D health state–based utilities to the time trade-off visual analogue scale method. The results were found to be sensitive to changes in time horizon, discount rate, treatment effect, and health utility method for patients in HY stage III, but were stable for patients in HY stage IV.

The stroke study undertook univariate sensitivity analysis when model assumptions and specifications regarding effect size, age of onset, aspects of the therapy provided, risk of stroke, and procedure-related mortality risk were varied to see their impact on the robustness of the results. SCT remained cost-effective, but there was a decrease in QALY gain with increased incremental costs associated with decrease in relative efficacy, higher age at stroke onset, and intervention in patients with higher disability (mRS score of 4), leading to lower societal value. SCT, however, remained cost-effective down to a relative efficacy size of 14%.

The SPMS study undertook a scenario analysis including optimistic, pessimistic, and middle-ground scenarios according to the assumption of the duration of sustained benefit and the method of measuring EDSS progression. The interpretation of clinical effectiveness (on the basis of different scenarios for measuring EDSS) had a significant impact on cost effectiveness. Univariate sensitivity analysis was also undertaken with varying model inputs such as the mortality rate associated with the intervention, treatment effect duration, cost of the intervention, cost of managing multiple sclerosis, and the discount rate.

Quality

Although all the studies performed univariate sensitivity analyses, the choice and range of variables examined were not explained in detail. Only the SPMS study explained why some variables were included. Although univariate sensitivity analysis is a valid approach, more sophisticated approaches can provide an indication of the impact of the overall uncertainty in the model when uncertainty around the model parameters exists (such as in the included studies). Approaches such as multiway analysis, threshold analysis, scenario analysis, and probabilistic sensitivity analysis can account for differences in multiple parameters at the same time and provide a more comprehensive picture of the total uncertainty in the findings [33].

Discussion

Main Findings

This is the first systematic review of published studies conducting economic evaluation of the use of SCT in neurological diseases. The studies included in our review differed in terms of disease indications, SCT types, clinical measures, evaluation perspectives, and cost outcomes included, which makes it difficult to compare results across the studies. All the included studies conducted a cost-utility analysis using early-stage health economic modeling. The models estimated the value proposition of SCT in disease populations over a long-term time horizon. All the studies reported potential cost savings over long-term and ongoing benefit in terms of decreased rate of disease progression and disability.

The individual studies examined different types of stem cells. The evidence from clinical research with SCT to date does not indicate that differences in cell types have a significant impact on effectiveness of therapy or safety. Having said that, the impact of using different cell types on potential clinical benefit (in terms of relative efficacy and safety) and thereby on cost effectiveness has not been specifically examined. This may reflect the early stage at which clinical research was at the time of publication of these studies [27]. As more studies are being conducted with distinctly characterized cell types, it may be possible in future to determine whether cell type should be a variable to examine in the cost-effectiveness analysis. There are uncertainties regarding the effect size of SCT, given the early stage of research and the inherent heterogeneity of disease characteristics, which make assessment of cost effectiveness complicated. Nevertheless, as newer data emerge regarding longer term clinical benefit with SCT, these models can be reworked with more substantive data to assess economic value and identify patient groups that are likely to maximally benefit.

Diseases such as stroke and PD contribute substantially to the health care budget [34,35]. Assessing effectiveness from this limited perspective may, however, underestimate the value of personalized interventions such as SCT. It fails to consider the potential gains in terms of decreased disability for the patients and increased participation in work and society. This is important to consider while assessing negotiated pricing strategies.

The quality of study methods and reporting is important because economic evaluations in this field are likely to grow. We assessed the quality of the reviewed studies using the CHEERS checklist [18]. None of the included studies fully satisfied all the criteria listed in the CHEERS checklist, with only 50% of the items being rated as "fully satisfied." Even though these studies were published before the formulation of the CHEERS checklist, the review highlights the need for incorporating these requirements in the conducting of and reporting for future economic evaluations of SCT.

Study Limitations

The included studies differed in terms of disease populations and SCT types. In addition, heterogeneity in terms of analytical methods, cost, and effectiveness measures used meant that only a narrative synthesis of findings is presented, because a formal meta-analysis was not appropriate.

Two of the three studies examined cost effectiveness from a government perspective only. Although this is key for determining future access strategy, economic evidence from a broad societal perspective may provide directions to optimize value by targeted research in specific patient groups and health care delivery pathways.

All the studies have sourced their effectiveness data from either single-arm studies, registry, or expert opinion. Although this may be acceptable for rare disease indications, effectiveness data in the more common neurological diseases such as stroke or PD may be more informative if adequately powered for the clinical outcome end points. A methodologically sound meta-analysis of smaller studies in future with appropriate sensitivity analysis may provide a reasonable early estimate of cost effectiveness. This, however, requires these studies to collect data on resource use in terms of effectiveness of the therapies in their study design. The models proposed in the studies included in the review may then be able to incorporate data from such analysis appropriately. The use of models is appropriate to the stage of research, and

these models are amenable to more extensive data inputs as they become available. Nevertheless, it is currently difficult to provide a detailed assessment of bias and generalizability of the findings of this review.

Potential Value of Health Economics Data at Early Drug Development

As research in regenerative medicine for neurological diseases approaches an exciting juncture, it becomes imperative to explore the associated cost outcomes [36]. This is critical to inform a targeted development strategy that maximizes chances of an eventual product that resonates with the value expectations for patients in need as well as for payers [37,38]. The focus on development efficiency is heightened by the constant shortening of the window of opportunity to realize returns on investments; research and development teams are faced with complex trade-offs in terms of developing an efficient product development strategy [39]. Early health economics data can provide useful input into defining these strategies.

Recommendations for Future Practice for Economic Evaluation in Regenerative Medicine

SCTs have been investigated in an increasing number of phase I and II trials across the globe for different neurological indications [6–9]. Incorporating cost outcomes into the research protocol at this stage will enable formative evidence to be generated and maximize the unique opportunity that stem cell research provides, in that these therapies are often researched in patient populations from the earliest stage rather than in healthy volunteers. The long-term persistence of the effects of SCT is a key consideration in choosing appropriate clinical and cost outcomes to calculate cost effectiveness [39,40]. A patient or societal perspective may be preferred because the high initial costs of SCT could be justified by ongoing cost savings because of sustained clinical improvement, improved independence, and participation in activities of daily life. This represents a more comprehensive measure of value. Participants in early-phase clinical studies with SCT are increasingly being followed over a longer time duration via extension studies or registries [40]. Collection of resource use data in these settings represents a useful means to examine cost effectiveness over longer durations. This will enable credible analysis of economic evidence and the complex trade-offs between investments during development and potential returns [35] and help manage access to these innovative therapies in a sustainable way.

Conclusions

Economic evaluation of SCT in neurological diseases is still at a nascent stage. Nevertheless, the recent progress in terms of clinical research underlines the urgent need to advance this field in tandem. Research to build economic evidence for cost effectiveness of these innovative therapies can potentially accelerate their clinical translation and provide channels for providing sustainable access to these therapies to patients in clinics.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.07.878.

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