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Relationship between volume of services and quality of treatment outcome for stem cell transplantations[1]

Extract

[1]Translation of Chapters 1 to 7 of the rapid report V18-02 *Zusammenhang zwischen Leistungsmenge und Qualität des Behandlungsergebnisses bei Stammzelltransplantationen* (Version 1.0; Status: 4 June 2019 [German original], 8 December 2019 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external expert and external reviewer is presented in Appendix C of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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Key statement

Research question

The aim of this investigation is to

present and assess the correlation between the volume of services and the quality of treatment outcome in allogeneic stem cell transplantation (SCT) in adults (research question 1a),

present and assess the correlation between the volume of services and the quality of treatment outcome in autologous SCT in adults (research question 1b), and

present and assess studies which investigate the effects of a minimum number of cases of SCT introduced into the healthcare system on the quality of treatment outcomes (research question 2).

Conclusion

For the investigation of a correlation between volume of services and quality of treatment outcome in haematopoietic SCT, a total of 4 registry studies were eligible for inclusion in the assessment. For 1 study, the informative value of results was rated as high. Among the outcomes relevant for the report, this study investigated only overall survival.

As regards the outcome of overall survival, the results with high informative value show, for both transplantation types, a significant increase with rising volume of services on the level of the treating physician after up to 1 year. This positive correlation between the volume of services and quality of treatment outcome is also shown for a follow-up period of 8 years by studies with low informative value of results; these studies considered the volume of services at the transplantation centre level.

For the other outcomes, only studies with low informative value of results were available. For the combined outcome of event-free survival after allogeneic SCT, a weak positive correlation between volume of services and event-free survival was derived only whenever the volume of services was defined disease-specifically for patients with chronic lymphatic leukaemia. A weak positive correlation between volume of services and non-relapse mortality after allogeneic SCT can also be derived for a follow-up period of 8 years. For shorter follow-up periods, the observed correlations are even weaker. In addition, a weak positive correlation between volume of services and relapse-free survival was found for allogeneic or autologous SCT as well as between volume of services and occurrence of relapse/progression for autologous SCT. In comparison, the observed correlation between the outcome of occurrence of relapse/progression after 5 or 6 years of follow-up, respectively, was weaker for allogeneic SCT.

No correlation was derived between volume of services and non-relapse mortality in autologous SCT or occurrence of relapse/progression in allogeneic SCT at a follow-up period of 8 years.

The included studies did not provide any usable data or did not report any data on other outcomes, such as acute or chronic graft-versus-host disease or quality of life.

No studies were found for investigating the effects of specific minimum case numbers implemented in patient care for SCT on the quality of treatment outcomes.

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List of abbreviations

Abbreviation	Meaning
ABMTR	Autologous Blood and Marrow Transplant Registry
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CLL	Chronic lymphatic leukaemia
CSI	Clinical severity index
EBMT	European Society for Blood and Marrow Transplantation
FACT	Foundation for the Accreditation of Cellular Therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GvHD	Graft-versus-host disease
HLA	Human leukocyte antigen
HR	Hazard ratio
IBMTR	International Bone Marrow Transplant Registry
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISCT	International Society for Cell & Gene Therapy
JACIE	Joint Accreditation Committee of ISCT-Europe & EBMT
NRM	Non-relapse mortality
OPS	Operationen- und Prozedurenschlüssel (operation and procedure code)
OR	Odds ratio
RCT	Randomized controlled trial
SCT	Stem cell transplantation
SGB	Sozialgesetzbuch (Social Code Book)
TRM	Treatment-related mortality

1 Background

Correlation between volume of services and quality of treatment outcome

As early as in 1979, Luft et al. examined the correlation between volume of services and quality of treatment outcome for 12 surgical procedures of different levels of complexity [1]. Their investigations showed that, for complex surgical procedures, there is a correlation between a hospital's volume of services and the quality of treatment outcome. In the following years, various studies showed a similar correlation for many medical services in different healthcare systems, with the volume of services being investigated per hospital and per physician [2–5].

The legal mandate of the Federal Joint Committee (G-BA) regarding minimum volume rules [6] is based upon the idea that there is a concrete connection between the probability of treatment success and the experience of the parties principally involved in rendering the service [6]. As part of quality assurance of registered hospitals, the G-BA therefore defines a catalogue of plannable services for which the quality of the treatment outcomes is dependent on the volume of services provided. This dependency is to be assessed on the basis of appropriate studies [7]. In December 2003, the G-BA for the first time set forth minimum volumes which are binding in Germany in accordance with §137 (3), Sentence 1, No. 2 Social Code Book V.

These minimum volume rules are binding for hospitals registered in accordance with §108 SBG V and specify in which cases a hospital may render the services for which minimum volumes have been set forth [8]. However, some exceptions apply. For instance, minimum volumes generally do not apply in cases of emergency. In addition, state authorities responsible for hospital planning can define exceptions for services where the implementation of minimum volume rules may jeopardize state-wide service provision to the population.

It is not easy to define services and specify minimum volume thresholds, in part due to the fact that multiple factors influence treatment success.

The current annual minimum volume for autologous/allogeneic bone marrow transplantation and peripheral haematopoietic stem cell transplantation (SCT) is 25 SCTs per hospital site [8].

Stem cell transplantation

Haematopoietic SCT is any procedure where haematopoietic, i.e. blood-forming cells of any source, are transferred from a donor to a recipient with the goal of completely or partially restoring blood formation [9]. It is a potentially curative treatment for many life-threatening cancers and some non-malignant diseases [10].

Allogeneic SCT is distinguished from autologous SCT, and both types of SCT are preceded by conditioning therapy.

Conditioning

Conditioning is typically performed in the form of chemotherapy or total body radiation therapy with or without chemotherapy. Myeloablative, non-myeloablative, and reduced-intensity regimens are distinguished based on their intensity.

Myeloablative conditioning pursues 3 main goals [11]:

- inducing myeloablation, i.e. creating room for the graft cells to engraft,
- inducing immunosuppression in the recipient to prevent graft rejection, and
- eradicating, i.e. decimating, malignant cells.

However, myeloablative conditioning is associated with considerable transplant-related mortality.

Non-myeloablative and reduced-intensity conditioning aim to achieve a balance between transplant-related mortality and the risk of another relapse. Their primary goal is immunosuppression [12, 13]. The reduced organ toxicity of non-myeloablative conditioning makes it possible to use allogeneic SCT in a larger patient population [11].

It is not possible to generally recommend a specific conditioning regimen for any disease entity. The intensity of conditioning should be chosen individually depending on comorbidities, age, remission status, risk of recurrence, and the extent of the graft-versus-tumour effect (donor immune cells attacking cancer cells), which varies by disease [14, 15].

Allogeneic stem cell transplantation

In allogeneic SCT, the patient receives stem cells from another, healthy person. Donor stem cells can be obtained from peripheral blood, bone marrow, or the umbilical cord. The prerequisite for transplantation is a close donor-patient match regarding human leukocyte antigen (HLA) markers, which are specific tissue markers on the surface of white blood cells. This is important, firstly to minimize the risk of a host-versus-graft reaction and secondly to minimize the attack of the donated bone marrow against the recipient's body (graft-versus-host disease [GvHD]) [16, 17]. HLA-identical relatives are usually preferred over HLA-compatible unrelated donors. Among relatives, siblings are considered first, because statistically, 1 in 4 siblings is HLA-identical.

The success of transplantation manifests, firstly, in the restoration of normal haematopoiesis in the bone marrow, called haematological reconstitution, and, secondly, in chimerism without further immunosuppression [18]. The goal is 100% donor chimerism, that is, blood formation being fully taken over by the donor's stem cells. Not reaching this 100% mark may be a sign of relapse or graft failure.

Autologous stem cell transplantation

In autologous SCT, stem cells are obtained from the patient and then reinfused at a later time. Typically, the stem cells are obtained from the peripheral blood. At the time the stem cells are obtained, the patient should be in remission. To achieve remission, the patient first receives induction chemotherapy for initial tumour cell reduction.

Before the patient is reinfused with his or her own stem cells, the patient is conditioned, typically using myeloablative therapy.

In autologous SCT, there is a risk of the transplantation causing damaged cells which survived chemotherapy to be reintroduced to the body, thus triggering a relapse. Contrary to allogeneic SCT, the advantage of autologous SCT lies in it not being associated with a risk of immunological complications such as graft-versus-host reaction or graft rejection.

2 Research question

The aim of this investigation is to

- present and assess the correlation between the volume of services and the quality of treatment outcome in allogeneic stem cell transplantation in adults (research question 1a),
- present and assess the correlation between the volume of services and the quality of treatment outcome in autologous stem cell transplantation in adults (research question 1b), and
- present and assess studies which investigate the effects of a minimum number of cases of stem cell transplantation introduced into the healthcare system on the quality of treatment outcomes (research question 2).

3 Course of the project

On 16 August 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) with a systematic literature search and evaluation of the evidence on the correlation between volume of services and quality of treatment outcome in stem cell transplantation.

On the basis of the project outline, a rapid report was generated and additionally subjected to an external review. This report was sent to the G-BA and published 4 weeks later on the IQWiG website.

4 Methods

Due to differences between the research questions, different methods were used in some cases.

4.1 Criteria for study inclusion in the investigation

4.1.1 Population

The assessment included studies with the following patients, broken down by research question:

- Research question 1a: adult patients treated with allogeneic haematopoietic SCT
- Research question 1b: adult patients treated with autologous haematopoietic SCT
- Research question 2: adult patients treated with allogeneic or autologous haematopoietic SCT

4.1.2 Volume of services

The volume of services was defined as the number of SCTs performed per hospital, per physician, or per hospital-physician combination within a defined time period.

4.1.3 Outcomes

For the investigation, the following outcomes were examined:

- Mortality
  - Overall survival
  - Treatment-related mortality (TRM) (including transplantation-associated mortality)
  - Non-relapse mortality (NRM)
- Morbidity
  - Disease-free survival (occurrence of relapse/progression)
  - Adverse effects of therapy such as
    - Serious or life-threatening GvHD or chronic GvHD (research questions 1 and 2)
    - Serious, life-threatening, or fatal infections
    - Occurrence of secondary neoplasms
    - Further serious treatment-related complications, if any
    - Serious adverse events
- Health-related quality of life, including activities of daily living and dependence on help from others

If usable data were found on other outcomes, they were permitted to be included as well.

4.1.4 Study types

Observational studies (e.g. cohort studies or case control studies) were suitable for answering research questions 1a and 1b since the statistical relationship between the volume of services and the occurrence of an event (see outcomes in Section 4.1.3) can be examined on the basis of these studies.

Adequately controlled interventional studies were suitable for answering research question 2. In this case, the intervention to be examined was the specification of a minimum volume. Possible comparator groups were groups with a different or no specified volume.

4.1.5 Adjustment

In SCT, the quality of the treatment outcome is decisively influenced by the primary disease and individual risk factors such as patient age, remission status, prior patient treatment, and, in allogeneic SCT, HLA match. Further indication-specific risk factors are possible.

Therefore, adequate control of confounders (risk adjustment) was a prerequisite for study inclusion. Adequate control was assumed to exist if the study analysis involved suitable statistical methods to adjust for relevant confounders in an effort to address the problem of potential structural inequalities (unfair comparisons) between hospitals or physicians with high and low volumes of services.

Likewise, cluster effects (e.g. greater similarity of outcomes in patients within the same hospital versus patients from different hospitals due to hospital-specific characteristics) had to have been taken into consideration by means of adequate statistical methods.

4.1.6 Study duration

There were no restrictions regarding the study duration.

4.1.7 Publication period

In accordance with the commission, studies with a publication date of January 2000 or later were included in the study.

4.1.8 Transferability

To ensure the transferability of study results to the German healthcare system, studies from European countries as well as the USA, Canada, Australia, and New Zealand were eligible for inclusion.

For international studies, at least 80% of the data had to come from the above countries.

4.1.9 Tabular presentation of the criteria for study inclusion

The tables below list the criteria which had to be met by studies included in the assessment.

Table 1: Overview of inclusion and exclusion criteria of studies for research questions 1a and 1b

Inclusion and exclusion criteria	
I1.1	Adult patients treated with ▪ allogeneic SCT (research question 1a) ▪ or autologous SCT (research question 1b) (also see Section 4.1.1)
I1.2	Investigation of the correlation between the volume of services and the quality of the treatment outcome
I1.3	Outcomes as formulated in Section 4.1.3
I1.4	Observational study as formulated in Section 4.1.4
I1.5	Adequate adjustment as formulated in Section 4.1.5
I1.6	Publication date of January 2000 or later
I1.7	Full publication available[a]
I1.8	Studies which are transferable to the German healthcare system (also see Section 4.1.8)
E1.1	Multiple publications without relevant additional information

a: In this context, a study report in accordance with ICH E3 [19] or a report about the study which met the criteria of the STROBE statement [20] and allowed an assessment of the study was considered a full publication, so long as the information on both the study methods and study results provided in these documents was not confidential.

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; SCT: stem cell transplantation; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

Table 2: Overview of inclusion and exclusion criteria of studies for research question 2

Inclusion and exclusion criteria	
I2.1	Adult patients treated with ▪ allogeneic or autologous SCT (research question 2) (also see Section 4.1.1)
I2.2	Study intervention: use of a minimum number of cases (also see Section 4.1.4)
I2.3	Comparator intervention: use of a different or no minimum number of cases (also see Section 4.1.4)
I2.4	Outcomes as formulated in Section 4.1.3
I2.5	Interventional study as formulated in Section 4.1.4
I2.6	Publication date of January 2000 or later
I2.7	Full publication available[a]
I2.8	Studies which are transferable to the German healthcare system (also see Section 4.1.8)
E2.1	Multiple publications without relevant additional information
a: In this context, a study report in accordance with ICH E3 [19] or a report about the study that met the criteria of the TREND statement [21] and allowed an assessment of the study was considered a full publication, so long as the information on both the study methods and study results provided in these documents was not confidential. ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; SCT: stem cell transplantation; TREND: Transparent Reporting of Evaluations with Nonrandomized Designs	

4.1.10 Inclusion of studies which do not fully meet the above criteria

For the inclusion criteria I1.1/I2.1 (population), I1.2 (volume of services), I2.2 (study intervention, with respect to the study's intervention group), and I2.3 (comparator intervention, with respect to the study' comparator group), it sufficed if at least 80% of included patients fulfilled these criteria. For such studies, subgroup analyses, if any, on patients who fulfilled the inclusion criteria were used. Studies in which inclusion criteria I1.1/I2.1, I1.2/I2.2, and I2.3 were fulfilled by fewer than 80% of patients were included only if subgroup analyses were available for patients who did fulfil the inclusion criteria.

4.2 Comprehensive information retrieval

4.2.1 Sources of information

For the comprehensive information retrieval, a systematic search was conducted for relevant studies or documents. The following primary and further information sources as well as search techniques were selected:

Primary information sources

- Bibliographic databases
  - MEDLINE
  - Embase
  - Cochrane Central Register of Controlled Trials
  - Cochrane Database of Systematic Reviews
  - HTA Database

Further information sources and search techniques

- Use of further search techniques
  - Screening of reference lists of systematic reviews found
- Requests to authors

4.2.2 Selection of relevant studies

Selection of relevant studies or documents from the results of the bibliographic search

In a first step, the titles and, if available, abstracts of the hits retrieved in the bibliographic databases were screened for potential relevance in terms of the inclusion criteria (see Table 1 and Table 2). In a second step, any documents considered potentially relevant were checked for relevance. Both steps were performed by 2 persons independently of each other. Any discrepancies were resolved by discussion between them.

Selection of relevant studies or documents from further information sources

Search results from the further information sources considered were screened for studies by 1 reviewer. The studies found were then checked for relevance. The whole process was then checked by a 2nd reviewer. Any discrepancies in one of the listed selection steps were resolved by discussion between the 2 reviewers.

4.3 Information synthesis and analysis

4.3.1 Presentation of the individual studies

All information needed for the investigation was extracted from the documents on the included studies and put into standardized tables. Any discrepancies found in connection with the comparison of information from different documents or from multiple data points within the same document, provided such discrepancies had the potential of considerably influencing the interpretation of results, are presented in the results section of the report.

Results were typically omitted from the investigation whenever they were based on fewer than 70% of the patients to be included in the analysis, that is, whenever more than 30% of patients were excluded from analysis.

Results were also omitted from the investigation whenever the percentage of patients excluded from analysis differed by more than 15% between groups.

4.3.2 Assessment of the informative value of results (research questions 1a and 1b)

For research questions 1a and 1b, the informative value of the results from the included observational studies was assessed on the basis of quality criteria developed especially for studies assessing volume-outcome correlations [22–25]. In terms of the informative value of results, the assessment considered the way the risk adjustment was performed, i.e., the risk factors taken into account and the sources used (administrative databases, clinical databases, medical records). Likewise, the quality of the statistical models used to examine the correlation between volume of services and outcome was assessed; this quality depends on the form in which the characteristic of volume entered into the analysis (continuous versus categorical data), on the consideration of cluster effects (see Section 4.1.5), and on the examination of model quality [26]. The completeness of reporting (e.g. description of analysed data and reporting of point estimates, confidence intervals, and p-values) was considered an aspect of the informative value of results as well. On the basis of the entirety of these quality criteria, the observational studies were categorized by quality into those with high versus low informative value.

4.3.3 Assessment of the risk of bias (research question 2)

For research question 2, the risk of bias of the results of the included controlled interventional studies was assessed in accordance with General Methods Version 5.0, Chapter 9 [27].

4.3.4 Summary assessment of information

The results on the outcomes reported in the studies were comparatively described in the report.

Beyond the comparison of results from the individual studies, suitable metaanalytical methods were to be used if possible [27]. A final summary assessment of the information was performed in any case.

5 Results

5.1 Comprehensive information retrieval

5.1.1 Primary information sources

5.1.1.1 Bibliographic databases

Figure 1 shows the results of the systematic literature search in the bibliographic databases and the study selection in accordance with the criteria for study inclusion. The search strategies for the search in bibliographic databases is found in Appendix A. The most recent search was conducted on 8 December 2018.

The references of the hits which were screened at full-text level but excluded are found in Section 9.2 of the full report, with the respective reason for exclusion.

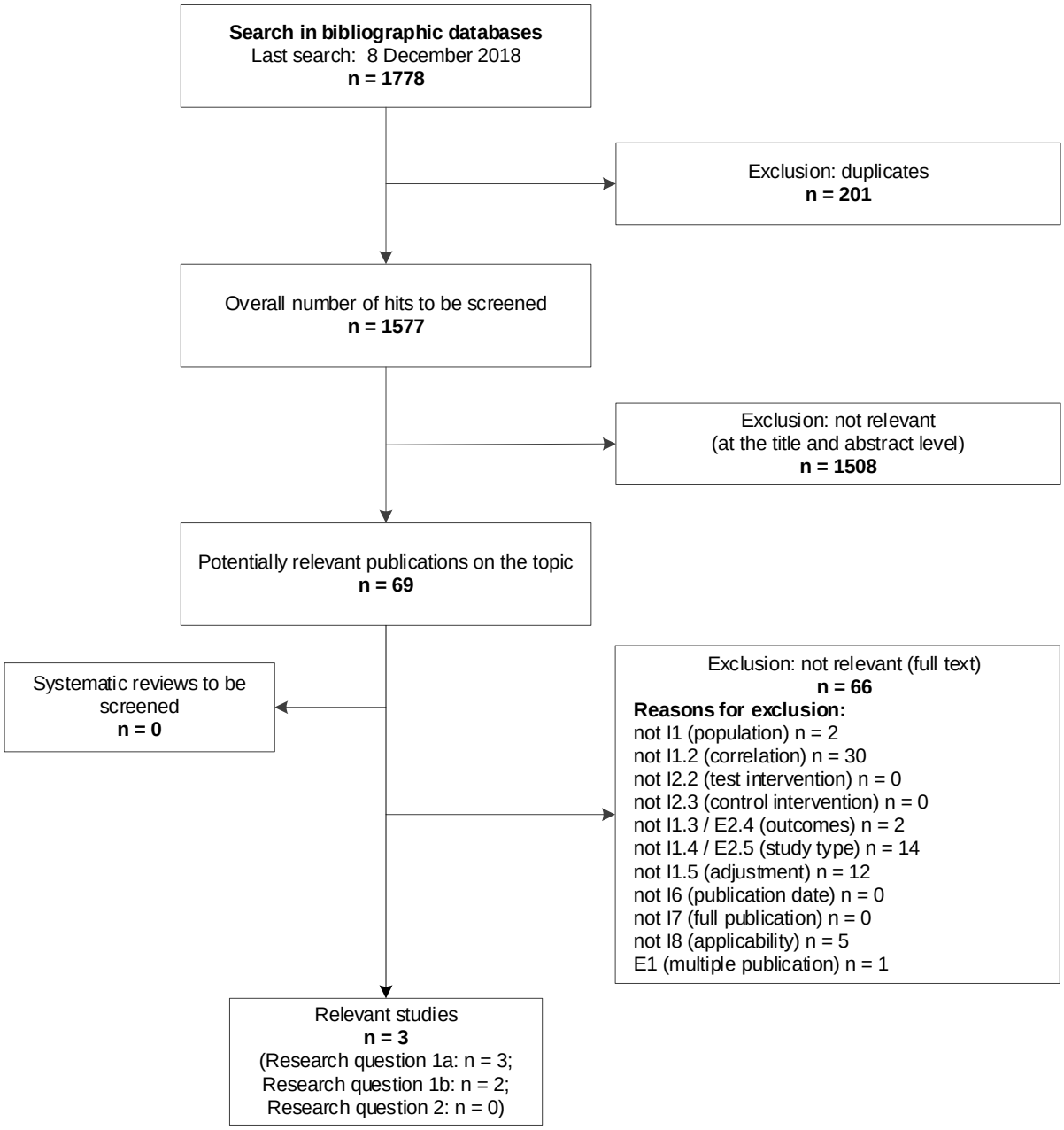

Figure 1: Result of the bibliographic search and study selection

5.1.2 Further information sources and search techniques

Relevant studies or documents found through further information sources and search techniques are presented below unless they were already found through primary information sources.

5.1.2.1 Application of further search techniques

The information retrieval did not find any relevant systematic reviews.

5.1.2.2 Requests to authors

No requests to authors to obtain additional information on relevant studies were necessary since such information was not expected to have a relevant impact on the assessment.

5.1.2.3 Further relevant studies

The following relevant study, which was not already identified in other search steps, was found (Table 3):

Table 3: Further relevant studies or documents found

Study	Available documents ([reference])	Relevant for
Gratwohl 2014	Full publication [28]	Research questions 1a and 1b

5.2 Resulting study pool

Through the various search steps, a total of 4 relevant studies were found (see also Table 4). The corresponding references are found in Section 9.1 of the full report. Four studies were available for answering research question 1a, and 3 studies were available for research question 1b. No controlled interventional studies were found to answer research question 2. The reasoning for excluding the other studies is documented in Section 9.2 of the full report.

Table 4: Study pool for research questions 1a and 1b

Study	Full publication (in professional journals)	Relevant for
Gratwohl 2015	Yes [29]	Research questions 1a and 1b
Gratwohl 2014	Yes [28]	Research questions 1a and 1b
Loberiza 2005	Yes [3]	Research questions 1a and 1b
Schetelig 2017	Yes [30]	Research question 1a

5.3 Characteristics of the studies included in the assessment

The included studies' report-relevant characteristics regarding research questions 1a and 1b are presented in Table 5 to Table 8 and summarized below.

Table 5: Characteristics of the included studies

Study/study design (data source)	Study objective	Follow-up period/transplantation period/recruitment country	Definition of VoS	Analysis of VoS/number of total units and, if applicable, per VoS category
Gratwohl 2015 Retrospective observational study (EBMT registry)	Influence of transplantation centre-specific and country-specific economic factors on the long-term treatment outcome of allogeneic or autologous SCT	Follow-up period: 8 years Transplantation period: 1 January 1999–31 December 2006 Most recent data collection: 1 January 2015 26 European countries (including Israel, Russia, and Turkey)[a]	Number of autologous or allogeneic SCTs with regard to the respective main indication per transplantation centre in the particular year of the SCT	Analysis: per increase in VoS by 10 patients TC total: 404 Patients total: 102 549 Allogeneic SCT: 37 542 Autologous SCT: 65 007
Gratwohl 2014 Retrospective observational study (EBMT registry)	Influence of JACIE accreditation on the treatment outcome of allogeneic or autologous SCT	Follow-up period: 6 years Transplantation period: 1 January 1999–31 December 2006 Recruitment countries not specified[b]	Number of autologous or allogeneic SCTs with regard to the respective main indication per transplantation centre in the year of the particular SCT	Analysis: per increase in VoS by 1 quartile[c] TC total: 585[d, e] **Allogeneic SCT:** Patients total: 41 623 1st quartile: 2199 2nd quartile: 5763 3rd quartile: 10 316 4th quartile: 23 345 **Autologous SCT:** Patients total: 66 281 1st quartile: 3938 2nd quartile: 10 005 3rd quartile: 18 286 4th quartile: 34 052

(continued)

Table 5: Characteristics of the included studies (continued)

Study/study design (data source)	Study objective	Follow-up period/transplantation period/recruitment country	Definition of volume of services	Analysis of VoS/number of total units and, if applicable, per VoS category
Loberiza 2005 Retrospective observational study (IBMTR and ABMTR Center Characteristics Surveys)	Influence of characteristics of the transplantation centre and the provider on overall survival after stem cell transplantation for treating a haematological disorder	Follow-up period: 100 days, 1 year Transplantation period: 1998-2000 United States of America	Number of allogeneic or autologous SCTs per physician within 1 year	Analysis: 2 categories, ≤ median of the annual VoS > median of the annual VoS **Allogeneic SCT:** TC total: 88 VoS ≤ 20 patients/1 MD: 36[e] (41%)[c] VoS > 20 patients/1 MD: 52[e] (59%)[c] Patients total: 1426 VoS ≤ 20 patients/1 MD: 762 (53%) VoS > 20 patients/1 MD: 664 (47%) **Autologous SCT:** TC total: 142 VoS ≤ 12 patients/1 MD: 71 (50%) VoS > 12 patients/1 MD: 71[e, f] (50%) Patients total: 2859 VoS ≤ 12 patients/1 MD: 646 (23%) VoS > 12 patients/1 MD: 2213 (77%)

(continued)

Table 5: Characteristics of the included studies (continued)

Study/study design (data source)	Study objective	Follow-up period/transplantation period/recruitment country	Definition of volume of services	Analysis of VoS/number of total units and, if applicable, per VoS category
Schetelig 2017 Retrospective observational study (EBMT registry and survey of the Data Quality Initiative)	Evaluation of inequalities of treatment outcomes in allogeneic stem cell transplantation in patients with chronic lymphatic leukaemia (CLL)	Follow-up period: 5 years Transplantation period: January 2000–December 2011 10 European countries	Number of allogeneic SCTs in general or in patients with CLL per transplantation centre in the two years prior to the respective SCT	Analysis: per increase in VoS by 1 patient in the two years prior to transplantation TC total: 30 Patients total: 684 VoS of allogeneic SCT in general within the study period: VoS ≤ 450 patients: 10 TC (33%) 334 patients[g] (192–448)[g] VoS 451–700 patients: 10 TC (33%) 516 patients[g] (452–589)[g] VoS > 700 patients: 10 TC (33%) 822 patients[g] (701–1690)[g] VoS of allogeneic SCT in patients with CLL: VoS < 20 patients: 12 TC (40%) 15 patients[g] (7–18)[g] VoS 20–34 patients: 10 TC (33%) 29 patients[g] (20–31)[g] VoS ≥ 35 patients: 8 TC (27%) 52 patients[g] (35–128)[g]

(continued)

Table 5: Characteristics of the included studies (continued)

a: The inclusion criterion I1.8 (transferability to the German healthcare system) is considered met.
b: According to information provided by Gratwohl 2015, the Gratwohl 2015 and Gratwohl 2014 studies are based on the same dataset, but they report different patient numbers.
c: The transplantation centres were categorized into successive quartiles on the basis of their VoS.
d: 162 accredited centres and 423 non-accredited centres.
e: IQWiG calculation.
f: Indicated in publication: 72 TCs. The total number of centres equals 142, and 50% of the centres are in each of the VoS categories.
g: Median.
h: Range.

ABMTR: Autologous Blood and Marrow Transplant Registry; CLL: chronic lymphatic leukaemia; EBMT: European Society for Blood and Marrow Transplantation; IBMTR: International Bone Marrow Transplant Registry; IQWiG: Institute for Quality and Efficiency in Health Care; ISCT: International Society for Cell & Gene Therapy; JACIE: Joint Accreditation Committee ISCT-Europe & EBMT; MD: specialist, physician, registrar; SCT: stem cell transplantation; TC: transplantation centre; VoS: volume of services

5.3.1 Study design and data source

A total of 4 cohort studies which are based on the data of clinical registries were included. Three studies are based on registry data from the European Society for Blood and Marrow Transplantation (EBMT) (Gratwohl 2015, Gratwohl 2014, Schetelig 2017) and 1 study on data from both the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry (ABMTR) (Loberiza 2005). These 3 registries contain data entered by the member centres on a voluntary basis after obtaining patient consent. The objective of these registries is to make available a data pool for studies and scientific exchange and to thereby improve patient survival, treatment, and quality of life [31, 32].

5.3.2 Objective of the studies

The studies Loberiza 2005 and Schetelig 2017 pursued the primary objective of investigating the correlation between the volume of services and treatment outcome. In the Gratwohl 2015 and Gratwohl 2014 studies, this parameter was investigated as one of several factors capable of influencing the treatment outcome.

Gratwohl 2015 builds upon the current discussion of minimum volumes and the call for objective measuring instruments for patient safety and treatment outcome. It investigates whether macroeconomic factors on the country level and microeconomic factors on the transplantation centre level influence the treatment outcome of haematopoietic SCT. On the transplantation centre level, it examines the influence of the volume of services, of the number of years for which transplantations have been performed, and of accreditation by the Joint Accreditation Committee of International Society for Cell & Gene Therapy ISCT Europe & EBMT (JACIE).

The Gratwohl 2014 study investigated the effects of the introduction of the JACIE quality management system on the treatment outcome of allogeneic or autologous SCT. The authors sought to answer the question whether the quality of the treatment outcome is favourably influenced by the introduction of a quality management system in a complex treatment such as SCT, which requires cooperation between a wide variety of providers. The number of annually conducted SCTs was investigated as one of the factors which might influence the treatment outcome of SCT.

The authors of the Loberiza 2005 study investigated whether factors other than the number of performed transplantations influence the treatment outcome. They explicitly abstained from limiting themselves to the volume of services per transplantation centre, but also looked at the influence of other transplantation centre characteristics as well as the influence of provider characteristics. Among other things, they investigated the influence of the number of SCTs performed by a physician on the quality of treatment outcome.

The objective of the Schetelig 2017 study was to quantify and explain the variability of treatment outcomes in allogeneic SCT in patients with chronic lymphatic leukaemia (CLL).

Although progress in the drug treatment of this disorder has been made in recent years, SCT remains an important additional treatment option in CLL.

5.3.3 Follow-up period and recruitment countries

The Gratwohl 2015 and Gratwohl 2014 studies are based on data from patients who received SCT between 1999 and 2006. In the Gratwohl 2015 study, the authors note that the same cohort was used as for Gratwohl 2014. However, the number of included patients differs between the studies. Thus, the two studies analyse a nearly identical data pool, but addressed different research questions. The Loberiza 2005 study is based on data from patients who received SCT between 1998 and 2000. Spanning from 2000 to 2011, the Schetelig 2017 study includes the most current data.

The Gratwohl 2015, Gratwohl 2014, and Schetelig 2017 studies are based on data of patients from European countries sending data to the EMBT registry. The Gratwohl 2015 study lists a total of 26 recruitment countries, including hospitals in Israel, Russia, and Turkey, which report to the EBMT registry. The Gratwohl 2014 study does not list the countries from which data of the EBMT registry were included. The Schetelig 2017 study analysed data from 10 European countries. The Loberiza 2005 study is the only one of the included studies to be based on data from hospitals located in the United States of America.

5.3.4 Definition of volume of services

The Gratwohl 2015 and Gratwohl 2014 studies define the volume of services as the number of allogeneic or autologous haematopoietic SCTs performed per transplantation centre with regard to the respective main indications in the year of transplantation. In the Gratwohl 2015 study, volume of services was analysed as a continuous variable, and the results were reported per increase in volume of services by 10 patients annually. In addition, the Gratwohl 2015 study used a categorical model. In contrast, Gratwohl 2014 considered the volume of services as a categorical variable and grouped the transplantation centres into successive quartiles by volume of services.

Like the Gratwohl 2015 and Gratwohl 2014 studies, the Schetelig 2017 study used the volume of services per transplantation centre, both in form of the number of allogeneic SCTs in general and in form of the number of allogeneic SCTs in patients with CLL in the two years prior to transplantation. The analysis considered the volume of services as a continuous variable, and the results were reported per increase in volume of services by one patient in the two years prior to transplantation.

In contrast, the Loberiza 2005 study defined the volume of services on the level of the treating physician, that is, as the number of allogeneic or autologous SCTs which the physician performed annually. Volume of services was treated as a categorical variable, and 2 categories based on the median were created for both allogeneic and autologous SCT. The median was 20 patients per year for allogeneic SCT and 12 patients per year for autologous SCT.

5.3.5 Study population

For allogeneic SCT, the number of included patients ranged from 684 (Schetelig 2017) to 41 623 (Gratwohl 2014), and for autologous SCT, from 2859 (Loberiza 2005) to 66 281 (Gratwohl 2014). The Gratwohl 2015 and Gratwohl 2014 studies report the total number of hospitals from which patient data were entered into the study, but not broken down by allogeneic versus autologous SCTs. The Gratwohl 2015 study included patients from a total of 404 hospitals, while Gratwohl 2014 included patients from 162 accredited hospitals and 423 non-accredited hospitals. The Schetelig 2017 study included only patients with CLL who were treated with allogeneic SCT; these patients came from 30 hospitals.

Table 6 below provides an overview of the primary diseases of the patients who were treated with allogeneic or autologous SCT in the respective studies.

Table 6: Overview of the primary diseases reviewed in the studies

Transplantation type / Study	**Primary haematological disease**					
	Acute leukaemia	**Chronic leukaemia**	**Malignant lymphoma**	**Plasma cell disease**	**Myelodysplastic syndrome / myeloproliferative neoplasm**	**Aplastic anaemia/ bone marrow failure syndrome**
Allogeneic SCT:						
Gratwohl 2015	●	●	●	●	●	-
Gratwohl 2014	●	●	●	●	●	●
Loberiza 2005	●	●	-	-	-	-
Autologous SCT						
Gratwohl 2015	●	●	●	●	●	-
Gratwohl 2014	●	●	●	●	●	●
Loberiza 2005	-	-	●	-	-	-
Schetelig 2017	-	●[a]	-	-	-	-

● Data on this primary disease were reported.
- No data were reported.
a: Exclusively chronic lymphatic leukaemia.
SCT: stem cell transplantation

Since the reporting of patient characteristics was very heterogeneous in the individual studies, the relevant characteristics were extracted separately for each study. The tables are presented in Section B.1 of the full report.

None of the included studies listed patient characteristics separately for individual volume of services categories. In the Loberiza 2005 study, the authors calculated a clinical severity index (CSI) for each patient – each time separately for allogeneic and autologous SCT and separately for the two outcomes considered in the study. This CSI included patient-related risk factors (age, sex, ethnicity), disease-related risk factors (primary disease, disease status, duration of illness, chemosensitivity in lymphomas) and transplantation-related risk factors (source of stem cells, total body radiation, GvHD prevention in allogeneic SCT, year of transplantation). No further information on patient characteristics or on the calculated CSIs are available from the study.

5.3.6 Inclusion and exclusion criteria

The main patient inclusion and exclusion criteria are listed in Table 7.

Table 7: Patient inclusion/exclusion criteria of the studies

Study	Main inclusion criteria	Main exclusion criteria
Gratwohl 2015	▪ Allogeneic or autologous SCT ▪ Primary disease as listed in Table 6 ▪ Disease status: first SCT ▪ Age: n.s.	▪ n.s.
Gratwohl 2014	▪ Allogeneic or autologous SCT ▪ Primary disease as listed in Table 6 ▪ Disease status: first SCT ▪ Age: n.s.	▪ n.s.
Loberiza 2005	▪ Allogeneic SCT with stem cells from an HLA-identical twin or autologous SCT ▪ Primary disease as listed in Table 6 ▪ Disease status: n.s. ▪ Age: > 18 years	▪ n.s.
Schetelig 2017	▪ Allogeneic SCT ▪ Primary disease as listed in Table 6 ▪ Disease status: first allogeneic SCT	Patients who ▪ already had Richter transformation ▪ received stem cells obtained from umbilical cord blood ▪ received a graft from a mismatched relative ▪ received a syngenic transplant
HLA: human leukocyte antigen; n.s.: not specified; SCT: stem cell transplantation		

5.3.7 Relevant outcomes

Data on relevant outcomes were extracted from all included studies. Table 8 presents an overview of the available data on relevant outcomes from the included studies.

In all studies, mortality served as an indicator of the quality of the treatment outcome. Gratwohl 2015, Gratwohl 2014, and Loberiza 2005 investigated the outcome of overall survival, while Schetelig 2017 reported data on the combined outcome of event-free survival, which comprises overall survival, relapse, or progression. In addition, the outcome of non-relapse mortality (Gratwohl 2015, Gratwohl 2014, Schetelig 2017) was investigated. In the Schetelig 2017 study, raw data on the outcomes of overall survival, acute GvHD, and chronic GvHD were reported, but they were unusable for the investigation due to the lack of risk adjustment. In Gratwohl 2015, Gratwohl 2014, and Schetelig 2015, data on disease-free survival (relapse/progression and relapse-free survival) was available as the only outcome on morbidity. The studies did not report any data on the outcome of health-related quality of life.

Table 8: Matrix of the relevant outcomes with reported results

Transplantation type / Study	**Outcomes**										
	Mortality				**Morbidity**						**QoL**
	Overall survival	**Event-free survival[b]**	**Treatment-related mortality**	**Non-relapse mortality**	**Disease-free survival (including relapse)**	**Severe, life-threatening, or fatal acute GvHD or chronic GvHD[a]**	**Serious, life-threatening, or fatal infections**	**Occurrence of secondary neoplasms**	**Further serious treatment-related complications**	**Serious adverse events**	**Health-related quality of life (instrument)**
Allogeneic SCT											
Gratwohl 2015	●	-	-	●	●	-	-	-	-	-	-
Gratwohl 2014	●	-	-	●	●	-	-	-	-	-	-
Loberiza 2005	●	-	-	-	-	-	-	-	-	-	-
Schetelig 2017	○	●	-	●	●	○	-	-	-	-	-
Autologous SCT											
Gratwohl 2015	●	-	-	●	●	-	-	-	-	-	-
Gratwohl 2014	●	-	-	●	●	-	-	-	-	-	-
Loberiza 2005	●	-	-	-	-	-	-	-	-	-	-

● Data were reported and were usable.
○ Raw data were reported but were not usable for the investigation.
- No data were reported.
a: This outcome is relevant exclusively for allogeneic SCT.
b: This combined outcome comprises overall survival as well as relapse and progression.
GvHD: graft-versus-host disease; QoL: health-related quality of life; SCT: stem cell transplantation

5.4 Assessment of the informative value of results (research questions 1a and 1b)

Table 9 presents the informative value of results. For the Loberiza 2005 study, the informative value of results was rated as high, while it was rated low for Gratwohl 2015, Gratwohl 2014, and Schetelig 2017.

The included studies used data from clinical registries. According to information provided by the authors, the studies Gratwohl 2015 and Gratwohl 2014 are based on the same dataset, but they report different patient numbers without any further explanation. Unlike the Gratwohl 2014 study, Gratwohl 2015 verified the completeness of the surveyed SCTs through reconciliation with audit data and with information from national organizations.

In all included studies, adequate risk adjustment was conducted on the level of the patient, the transplantation method, and transplantation centre. Table 10 shows an overview of the relevant risk factors which were taken into account in the studies.

In the Loberiza 2005 study, multivariate logistic regression was used for risk adjustment, while Gratwohl 2015, Gratwohl 2014, and Schetelig 2017 employed a multivariate Cox proportional hazards regression model. The correlation between the volume of services and the quality of treatment outcome was modelled continuously in Gratwohl 2015 and Schetelig 2017 and categorically in Loberiza 2005 and Gratwohl 2014. In Gratwohl 2015, a categorical model was used alongside the continuous model. Since categorical analysis is associated with a loss of information (e.g. the linearity assumption is violated within the individual categories) and might deliver less reliable results than continuous analysis [25], only the results of continuous modelling were included in the report if results were available from both continuous as well as categorical modelling. Moreover, the presentation of results for categorical analysis in the Gratwohl 2015 study would be incomplete.

Cluster effects were taken into account in all included studies. Gratwohl 2014, Loberiza 2005, and Schetelig 2017 described the statistical methods used to account for cluster effects. In Gratwohl 2015, no detailed information is provided on the method used.

None of the included studies provided information on a check of model quality or validation of the statistical model.

In Gratwohl 2015, Loberiza 2005, and Schetelig 2017, the point estimates, confidence intervals, and p-values are indicated, while the latter are missing in Gratwohl 2014. In Schetelig 2017, discrepant information was provided on the reference value for the calculation of the volume of services.

Due to the availability of ample pertinent data, the high-quality data analysis, and complete reporting, the informative value of Loberiza 2005 was rated as high.

Table 9: Informative value of results

Study	High quality of individual data	Adequate patient flow	Volume analysis	Plausible procedure for determining the volume threshold	Suitable model class	Adequate procedure to account for cluster effects	Adequate risk adjustment on all levels	Adequate handling of missing data	Information on a check of model quality	Model validation	Information on effect estimate including precision	Adequate reporting of relevant aspects	Further aspects	Informative value of results
Gratwohl 2015	Unclear	No	Continuous[a]	Yes	Yes	Unclear	Yes	Unclear	No	Unclear	Yes	Yes	Investigation of volume/outcome was not a primary study objective Voluntary participation in EBMT registry Gratwohl 2014 reports different patient numbers despite using the same underlying data.	Low
Gratwohl 2014	No[b]	No	Categorical	Yes	Yes	Yes	Yes	Unclear	No	Unclear	In part[c]	Yes	Investigation of volume/outcome was not a primary study objective Voluntary participation in EBMT registry	Low
Loberiza 2005	Yes	Yes	Categorical	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	Yes	Voluntary participation in IBMTR and ABMTR	High
Schetelig 2017	Unclear	Yes	Continuous	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	No[d]	Voluntary participation in EBMT registry	Low

(continued)

Table 9: Informative value of results (continued)

a: The study additionally presents a categorical analysis, whose results were not used for this report.
b: In Gratwohl 2014, unlike Gratwohl 2015, the completeness of recorded SCTs was not verified by reconciliation with other data sources.
c: No p-values specified.
d: Discrepant information provided in the publication on the reference value for calculation of the VoS, among other things.

ABMTR: Autologous Blood and Marrow Transplant Registry; EBMT: European Society for Blood and Marrow Transplantation; IBMTR: International Bone Marrow Transplant Registry; VoS: volume of services

Table 10: Matrix of relevant risk factors taken into account in the adjustment

Study	Risk factors																								
	Patient												Transplantation method							Transplantation centre				
	Primary disease	Age	Sex	Ethnicity	EBMT risk score	Disease status	Duration of illness	Karnofsky index	Remission status	Prior autologous stem cell transplantation	Sensitivity to chemotherapy (autologous)	Cytogenetic abnormalities	Year transplantation was performed	Conditioning	GvHD prophylaxis (allogeneic)	Donor type (allogeneic)	Donor-recipient sex constellation	Stem cell source	T-cell depletion	Accreditation	SCT program duration	Affiliation with medical school	Initial contact in emergencies/after hours	Gross national income per capita
Gratwohl 2015	●	●	-	-	●	○	-	-	-	-	-	-	●	●	-	○	○	-	-	●	●	-	-	-
Gratwohl 2014	●	●	-	-	●	○	-	-	-	-	-	-	●	●	-	○	○	-	-	●	-	-	-	●
Loberiza 2005	●	●	●	●	-	●	●	-	-	-	●	-	●	●	●	●	-	-	-	-	-	●	●	-
Schetelig 2017	x	●	-	-	-	-	-	●	●	●	-	●	●	●	-	●	●	●	●	●	-	-	-	●

● Risk factor taken into account in the adjustment.
○ Risk factor included in EBMT risk score. The latter includes the factors of age of the patient, disease stage, time from diagnosis to transplantation, donor type, and donor-recipient sex constellation.
x Risk factor irrelevant for study since the study refers to only 1 primary disease.
- No adjustment made for this risk factor.

5.5 Results on relevant outcomes

The results on the outcomes relevant for the report are presented below. The results are presented separately for allogeneic SCT (research question 1a) and autologous SCT (research question 1b).

5.5.1 Results on overall survival

Results on the outcome of overall survival were reported in the study with high informative value of results (Loberiza 2005) and in 2 studies with low informative value of results. The Schetelig 2017 study data on this outcome were not usable (see Section 5.3.7).

Allogeneic SCT

In the Loberiza 2005 study (with high informative value of results), a statistically significant association was reported between volume of services per physician and overall survival (see Table 11). Overall survival after 100 days or 1 year was higher if the transplantation was performed by a physician with a volume of services of more than 20 patients annually rather than by a physician with a lower volume of services.

Table 11: Results – overall survival after allogeneic stem cell transplantation (binary)

Study	Time after transplantation	N	OS raw n (%)	Information on VoS (per physician)	Adjusted odds ratio [95% CI]; p-value
Loberiza 2005	100 days	1426[a]	n.s.	> 20 vs. ≤ 20 patients	0.67 [0.51; 0.88]; 0.003[b]
	1 year	1426[a]	n.s.	> 20 vs. ≤ 20 patients	0.78 [0.63; 0.98]; 0.03[b]

a: 664 patients were treated by a physician who transplants > 20 patients annually, and 762 patients by a physician who transplants ≤ 20 patients annually.
b: Chi-square test.
CI: confidence interval; N: number of analysed patients; n: number of patients with an event; n.s.: not specified; OS: overall survival; VoS: volume of services; vs.: versus

Similarly, in the Gratwohl 2015 and Gratwohl 2014 studies, both with low informative value of results, the overall survival reported for allogeneic SCT after 8 or 6 years, respectively, was statistically significantly higher for transplantation centres with a higher volume of services (see Table 12).

Table 12: Results – overall survival after allogeneic stem cell transplantation

Study	Time after transplantation	N	OS raw n (%)	Information on VoS (per TC)	Adjusted hazard ratio [95% CI]; p-value
Gratwohl 2015	8 years	37 542	16 143[a] (43)	Per increase by 10 patients annually	0.87 [0.84; 0.91]; < 0.001[b]
Gratwohl 2014	6 years	41 623	19 563[a] (47)	Per increase by 1 quartile	0.95 [0.92; 0.98]; < 0.05[b]

a: IQWiG calculations.
b: Test unclear.
CI: confidence interval; IQWiG: Institute for Quality and Efficiency in Health Care; N: number of analysed patients; n: number of patients with an event; OS: overall survival; TC: transplantation centre; VoS: volume of services

The correlation between volume of services per physician and the outcome of overall survival reported in the Loberiza 2005 study was considerably stronger 100 days after transplantation than 1 year after transplantation. In contrast, the two other studies showed a less pronounced correlation between the volume of services (per transplantation centre) 6 years after transplantation (Gratwohl 2014) than 8 years after transplantation (Gratwohl 2015).

Autologous SCT

In the Loberiza 2005 study with a high informative value of results, a statistically significantly higher overall survival after 100 days or 1 year was reported if the transplantation was performed by a physician with a volume of services of more than 12 patients per year, in comparison with transplantations performed by physicians with a lower volume of services (see Table 13).

Table 13: Results – overall survival after autologous stem cell transplantation (binary)

Study	Time after transplantation	N	OS raw n (%)	Information on VoS (per physician)	Adjusted odds ratio [95% CI]; p-value
Loberiza 2005	100 days	2859[a]	n.s.	> 12 vs. ≤ 12 patients	0.74 [0.57; 0.98]; 0.03[b]
	1 year	2859[a]	n.s.	> 12 vs. ≤ 12 patients	0.82 [0.67; 0.99]; 0.04[b]

a: 2213 patients were treated by a physician who transplants > 12 patients annually, and 646 patients by a physician who transplants ≤ 12 patients annually.
b: Chi-square test.
CI: confidence interval; N: number of analysed patients; n: number of patients with an event; n.s.: not specified; OS: overall survival; VoS: volume of services; vs.: versus

Similarly, in the Gratwohl 2015 and Gratwohl 2014 studies, the overall survival reported for autologous SCT after 8 years or 6 years, respectively, was statistically significantly higher for transplantation centres with a higher annual volume of services as well (see Table 14).

Table 14: Results – overall survival after autologous stem cell transplantation

Study	Time after transplantation	N	OS raw n (%)	Information on VoS (per TC)	Adjusted hazard ratio [95% CI]; p-value
Gratwohl 2015	8 years	65 007	33 154[a] (51)	Per increase by 10 patients annually	0.91 [0.87; 0.96]; < 0.001[b]
Gratwohl 2014	6 years	66 281	37 780[a] (57)	Per increase by 1 quartile	0.95 [0.94; 0.97]; n.s.

a: IQWiG calculations.
b: Test unclear.
CI: confidence interval; IQWiG: Institute for Quality and Efficiency in Health Care; N: number of analysed patients; n: number of patients with an event; n.s.: not specified; OS: overall survival; TC: transplantation centre

In summary, one study with high informative value of results showed a clearly positive correlation between volume of service per physician and the outcome of overall survival for both allogeneic and autologous SCT. Two studies with a low informative value of results support these findings for the volume of services on the level of the transplantation centre.

5.5.2 Results on the combined outcome of event-free survival

In the study with high informative value of results (Loberiza 2005), no results on the outcome of event-free survival were reported. The Schetelig 2017 study with a low informative value of results reported results for allogeneic SCT in patients with CLL. The combined outcome of event-free survival comprises the events of overall survival and occurrence of relapse or progression.

Allogeneic SCT

In the Schetelig 2017 study, event-free survival was reported to be statistically significantly higher at an increasing volume of services if the volume of services is defined as the number of allogeneic SCTs performed in patients with CLL at the transplantation centre in the past 2 years. In contrast, the volume of services as measured by the total of allogeneic SCTs performed at the transplantation centre did not influence event-free survival (see Table 15).

Table 15: Results – event-free survival after allogeneic stem cell transplantation

Study	Time after transplantation	N	EFS raw n (%)	Information on VoS (per TC)	Adjusted hazard ratio [95% CI]; p-value
Schetelig 2017	5 years	684	253[a] (37[b])	Per increase by 1 allogeneic SCT patient[c]	1.00 [–][d]; 0.2[e]
				Per increase by 1 allogeneic SCT patient with CLL[c]	0.96 [0.93; 0.98]; 0.002[e]

a: IQWiG calculations.
b: 95% CI [34; 42].
c: Referring to the two years prior to transplantation.
d: Data unusable due to unfavourable unit and associated rounding.
e: Test unclear.
CI: confidence interval; CLL: chronic lymphatic leukaemia; EFS: event-free survival; IQWiG: Institute for Quality and Efficiency in Health Care; N: number of analysed patients; n: number of patients with an event; SCT: stem cell transplantation; TC: transplantation centre; VoS: volume of services

In summary, in one study with low informative value of results, the volume of services was analysed on the transplantation centre level, both on the basis of the number of all allogeneic SCTs performed at the transplantation centre and disease-specifically on the basis of the number of allogeneic SCTs performed in patients with CLL. A weak positive correlation between volume of services and event-free survival was reported only whenever the volume of services was defined disease-specifically.

In contrast, for the outcome component of occurrence of relapse/progression, which is part of the combined outcome of event-free survival, it was not possible to derive a correlation with volume of services (see Section 5.5.5). For the outcome component of overall survival, no data were usable (see Section 5.3.7).

5.5.3 Results on treatment-associated mortality

Results on treatment-associated mortality were not reported in any of the included studies.

5.5.4 Reports on non-relapse mortality

Results on the outcome of non-relapse mortality were not reported in the study with high informative value of results (Loberiza 2005), but in 3 studies with low informative value of results.

Allogeneic SCT

Gratwohl 2015 reported a statistically significant but small decrease in non-relapse mortality with increasing annual volume of services of the transplantation centre over a period of 8 years. In the Gratwohl 2014 study with 6 years of follow-up as well as in the Schetelig 2017 study with 5 years of follow-up, the results go in the same direction, but are close to the null effect. (see Table 16).

Table 16: Results – non-relapse mortality after allogeneic stem cell transplantation

Study	Time after transplantation	N	NRM raw n (%)	Information on VoS (per TC)	Adjusted hazard ratio [95% CI]; p-value
Gratwohl 2015	8 years	37 542	11 263[a] (30)	Per increase by 10 patients annually	0.86 [0.82; 0.91]; n.s.
Gratwohl 2014	6 years	41 623	12 071[a] (29)	Per increase by 1 quartile	0.95 [0.91; 1.00]; n.s.
Schetelig 2017	5 years	684	239[a] (35[b])	Per increase by 1 allogeneic SCT patient[c]	1.00 [–][d]; 0.7[e]
				Per increase by 1 allogeneic SCT patient with CLL[c]	0.96 [0.93; 0.99]; 0.005[e]

a: IQWiG calculations.
b: 95% CI [31; 39].
c: Referring to the two years prior to transplantation.
d: Data unusable due to unfavourable unit and associated rounding.
e: Test unclear.

CI: confidence interval; CLL: chronic lymphatic leukaemia; IQWiG: Institute for Quality and Efficiency in Health Care; N: number of analysed patients; n: number of patients with event; NRM: non-relapse mortality; n.s: not specified; SCT: stem cell transplantation; TC: transplantation centre; VoS: volume of services

Autologous SCT

For autologous SCT, the Gratwohl 2015 and Gratwohl 2014 studies show no correlation between the volume of services of the transplantation centre and non-relapse mortality (see Table 17).

Table 17: Results – non-relapse mortality after autologous tem cell transplantation

Study	Time after transplantation	N	NRM raw n (%)	Information on VoS (per TC)	Adjusted hazard ratio [95% CI]; p-value
Gratwohl 2015	8 years	65 007	8451[a] (13)	Per increase by 10 patients	0.96 [0.87; 1.07]; n.s.
Gratwohl 2014	6 years	66 281	7291[a] (11)	Per increase by 1 quartile	1.00 [0.97; 1.03]; n.s.

a: IQWiG calculations.

CI: confidence interval; IQWiG: Institute for Quality and Efficacy in Health Care; N: number of analysed patients; n: number of patients with event; NRM: non-relapse mortality; n.s.: not specified; TC: transplantation centre; VoS: volume of services

In summary, for allogeneic SCT, one study with low informative value of results showed a weak positive correlation between volume of services per transplantation centre and non-relapse mortality 8 years after transplantation. In 2 other studies with low informative value of results and shorter follow-up periods, the correlations observed for allogeneic SCT were even less pronounced. For autologous SCT, the results show no correlation between volume of services and non-relapse mortality.

5.5.5 Results on disease-free survival

The study with high informative value of results (Loberiza 2005) did not report any results on disease-free survival. Among the studies with low informative value of results, 2 studies reported results on the outcome of relapse-free survival, and 3 studies reported results on the outcome of occurrence of relapse/progression.

Allogeneic SCT

In the studies Gratwohl 2015 and Gratwohl 2014, a statistically significant but small increase of disease-free survival after allogeneic SCT was reported with increasing volume of services of the transplantation centre (see Table 18). For the occurrence of relapse/progression, the results of the studies Gratwohl 2015, Gratwohl 2014, and Schetelig 2017 go in the same direction, but without a (clear) statistical significance of effects (see Table 19).

Table 18: Results – relapse-free survival after allogeneic stem cell transplantation

Study	Time after transplantation	N	RFS raw n (%)	Information on VoS (per TC)	Adjusted hazard ratio [95% CI]; p-value
Gratwohl 2015	8 years	37 542	13 891[a] (37)	Per increase by 10 patients annually	0.92 [0.88; 0.96]; < 0.05[b]
Gratwohl 2014	6 years	41 623	16 649[a] (40)	Per increase by 1 quartile	0.96 [0.94; 0.99]; n.s.

a: IQWiG calculations.
b: Test unclear.
CI: confidence interval; IQWiG: Institute for Quality and Efficiency in Health Care; N: number of analysed patients; n: number of patients with event; n.s.: not specified; RFS: relapse-free survival; TC: transplantation centre; VoS: volume of services

Table 19: Results – relapse/progression after allogeneic stem cell transplantation

Study	Time after transplantation	N	RI raw n (%)	Information on VoS (per TC)	Adjusted hazard ratio [95% CI]; p-value
Gratwohl 2015	8 years	37 542	12 389[a] (33)	Per increase by 10 patients annually	0.98 [0.92; 1.04]; n.s.
Gratwohl 2014	6 years	41 623	12 487[a] (30)	Per increase by 1 quartile	0.97 [0.93; 1.00]; n.s.
Schetelig 2017	5 years	684	192[a] (28[b])	Per increase by 1 allogeneic SCT patient[c]	1.00 [–][d]; 0.2[e]
				Per increase by 1 allogeneic SCT patient with CLL[c]	0.96 [0.9; 1.00]; 0.06[e]

a: IQWiG calculations.
b: 95% CI [24; 31].
c: Referring to the two years prior to transplantation.
d: Data not usable due to unfavourable unit and associated rounding.
e: Test unclear.

CI: confidence interval; CLL: chronic lymphatic leukaemia; IQWiG: Institute for Quality and Efficiency in Health Care; N: number of analysed patients; n: number of patients with an event; n.s: not specified; RI: recurrence incidence; SCT: stem cell transplantation; TC: transplantation centre; VoS: volume of services

Autologous SCT

In the studies Gratwohl 2015 and Gratwohl 2014, a statistically significant but small increase of relapse-free survival after autologous SCT was reported with increasing volume of services of the transplantation centre (see Table 20). For the occurrence of relapse, these studies reported a statistically significant, but small decrease with increasing volume of services (see Table 21).

Table 20: Results – relapse-free survival after autologous stem cell transplantation

Study	Time after transplantation	N	RFS raw n (%)	Information on VoS (per TC)	Adjusted hazard ratio [95% CI]; p-value
Gratwohl 2015	8 years	65 007	22 752[a] (35)	Per increase by 10 patients annually	0.93 [0.89; 0.97]; < 0.05[b]
Gratwohl 2014	6 years	66 281	26 512[a] (40)	Per increase by 1 quartile	0.95 [0.94; 0.97]; n.s.

a: IQWiG calculations.
b: Test unclear.

CI: confidence interval; IQWiG: Institute for Quality and Efficiency in Health Care; N: number of analysed patients; n: number of patients with event; n.s.: not specified; RFS: relapse-free survival; TC: transplantation centre; VoS: volume of services

Table 21: Results – relapse after autologous stem cell transplantation

Study	Time after transplantation	N	RI raw n (%)	Information on VoS (per TC)	Adjusted hazard ratio [95% CI]; p-value
Gratwohl 2015	8 years	65 007	34 454[a] (53)	Per increase by 10 patients annually	0.92 [0.87; 0.98]; n.s.
Gratwohl 2014	6 years	66 281	32 478[a] (49)	Per increase by 1 quartile	0.94 [0.93; 0.96]; n.s.

a: IQWiG calculations.

CI: confidence interval; IQWiG: Institute for Quality and Efficiency in Health Care; N: number of analysed patients; n: number of patients with an event; n.s.: not specified; RI: recurrence incidence; TC: transplantation centre; VoS: volume of services

In summary, in 2 studies with low informative value of results, the observed correlations between transplantation centre volume of services and relapse-free survival went in the same direction and showed, at most, a weak positive correlation for both allogeneic SCT and autologous SCT. For allogeneic SCT, 3 studies with low informative value of results revealed an even less pronounced, if any, correlation between volume of services and occurrence of relapse/progression. In contrast, 2 studies with low informative value of results showed a weak positive correlation between the volume of services and occurrence of relapse/progression for autologous SCT.

5.5.6 Results on adverse effects of therapy

The included studies did not report any results on adverse effects of therapy relevant for this report. The Schetelig 2017 study reported only non-adjusted results on the outcomes of acute and chronic GvHD, rendering the results presented in the study unusable.

5.5.7 Results on health-related quality of life

Results on health-related quality of life were not reported in any of the included studies.

5.6 Overall evaluation of results

One study with high informative value of results showed a clearly positive correlation between physician volume of services and the outcome of overall survival for both allogeneic and autologous SCT. Studies with low informative value of results support these findings for the volume of services at the transplantation centre level.

Results on the other outcomes were reported exclusively by the studies with low informative value of results:

For the combined outcome of event-free survival in allogeneic SCT, a weak positive correlation between transplantation centre volume of services and event-free survival was reported only whenever the volume of services was defined disease-specifically for CLL patients. A weak positive correlation was also reported for the outcome of non-relapse mortality in allogeneic

SCT 8 years after transplantation, for the outcome of relapse-free survival in allogeneic or autologous SCT, and for the outcome of occurrence of relapse/progression in autologous SCT.

For the outcome of non-relapse mortality and the outcome of occurrence of relapse/progression in allogeneic SCT with a follow-up period of 5 or 6 years, respectively, an even weaker positive correlation between volume of services and the outcome was reported.

For the outcome of non-relapse mortality in autologous SCT and for the outcome of occurrence of relapse/progression in allogeneic SCT with a follow-up period of 8 years, it was not possible to derive a correlation between volume of services and the respective outcome.

In the included studies, no usable data were available on the outcome of GvHD, and none of the studies reported results on the outcome of health-related quality of life.

Table 22 below summarizes the results of the included studies on the relevant outcomes.

Table 22: Overview: Correlation between volume of services and outcomes

	Mortality				**Morbidity**						**QoL**
	Overall survival	**EFS**	**Treatment-related mortality**	**Non-relapse mortality**	**Disease-free survival**		**Serious, life-threatening, or fatal aGvHD or cGvHD[a]**	**Serious, life-threatening, or fatal infections**	**Occurrence of secondary neoplasms**	**Further serious treatment-related complications**	**Serious adverse events**	**Health-related quality of life (instrument)**
					RFS	**RI**						
Allogeneic SCT	↑[b]	(↑)[c, d]	-	(↑)[c]	(↑)[c]	(↔)[c]	-	-	-	-	-	-
Autologous SCT	↑[b]	-	-	(↔)[c]	(↑)[c]	(↑)[c]	-	-	-	-	-	-

↑ Statistically significantly higher quality of treatment outcome in case of higher VoS (1 study with high informative value of results)
(↑) Exclusively results of low informative value are available, at least some of them reporting a statistically significantly higher quality of treatment outcomes in case of higher VoS.
(↔) Exclusively results of low informative value are available which are not statistically significant.
- The included studies did not report any usable results on this outcome.
a: This outcome is relevant exclusively for allogeneic SCT.
b: VoS determined at the physician level.
c: VoS determined at the transplantation centre level.
d: Correlation applies only to the disease-specific definition of VoS.
aGvHD: acute graft-versus-host disease; cGvHD: chronic graft-versus-host disease; EFS: event-free survival; QoL: health-related quality of life; RFS: relapse-free survival; RI: recurrence incidence; SCT: stem cell transplantation; VoS: volume of services

6 Discussion

Influence of volume of services on the quality of treatment outcomes (research questions 1a and 1b)

This report aimed to present and assess a potential correlation between the volume of services and the quality of treatment outcomes in stem cell transplantation. The G-BA commissioned the report against the backdrop of consultations on minimum volume rules in force for the transplantation of haematopoietic stem cells from bone marrow and the transfusion of peripherally obtained haematopoietic stem cells.

The minimum volume rules for SCTs in Germany apply per hospital site. In this report, a total of 4 studies were included, only 1 of which had a high informative value of results (Loberiza 2005). The latter study showed a clear correlation between the volume of services and overall survival. However, the study defined the volume of services per physician, that is, it investigated the influence of the experience of a single physician on the quality of the treatment outcome. On the basis of the results from this study, a minimum volume could therefore be justified per physician, but not per transplantation centre.

Further, there is not a simple causal relationship between the volume of services and the quality of treatment outcome, but rather, this is part of a multicausal constellation. An increasing volume of services strengthens the experience not only of the physician performing transplantation, but also of the entire team involved in patient care. Simultaneously, a larger volume of services is associated, for instance, with a more frequent occurrence of unusual disease courses or rare complications; therefore, as the volume of services increases, so does experience in early detection, prevention, and treatment of such rare and critical situations [33].

The challenge lies in determining the influence of the volume of services independently from further influencing factors.

Adequate adjustment

Risk adjustment

Factors influencing the quality of the treatment outcome include the risk factors established with regard to the patient (e.g. age, sex), disease (e.g. primary disease, disease status, duration of illness), and transplantation procedure (e.g. prior treatment of patient, year of transplantation, HLA matching). Adequate risk adjustment was therefore a prerequisite for a study's inclusion in the report. In the Schetelig 2017 study, which was included in the report, only raw data without risk adjustment were reported for the outcomes of overall survival and acute or chronic GvHD. Consequently, the results on these outcomes were not usable for the report.

To meet the inclusion criterion of adequate risk adjustment, the studies had to rely on a correspondingly comprehensive data basis, however. Due to a lack of adequate risk adjustment, it was not possible to include 2 studies which are based on the German health care context and on data from the DRG-based hospital statistics [34, 35]. The data of this database were collected

and documented for a different purpose. For this reason, the registry lacks important, relevant medical parameters, thereby negatively influencing the quality of the risk adjustment model [36]. In terms of potential risk factors, both studies considered patient age, sex, and primary disease/comorbidities. As the only disease for which SCT is a relevant indication, Nimptsch et al. included acute leukaemia in their analysis. According to the EBMT registry, 23% of all documented SCTs were performed due to this indication in 2007 [37]. Neither of the two studies considered further important risk factors in accordance with the EBMT risk score [38], particularly disease status and, unless transplantation is performed in 1st full remission, the time from diagnosis to transplantation and, in case of allogeneic transplantation, donor type, and donor-recipient sex constellation. In addition, both studies aggregated all documented OPS codes related to the minimum volume rule on the hospital level rather than separately collecting them for allogeneic versus autologous SCT. Therefore, it was not possible to use these studies to answer research question 1a or 1b, which are specific to the transplantation type.

Three of the studies included in the report used the EBMT registry for their analyses (Gratwohl 2015, Gratwohl 2014, and Schetelig 2017). This registry did not include any information on patient comorbidities, a risk factor which has gained in importance in recent years. This is because, as a result of the option of non-myeloablative or reduced-intensity conditioning, the number of allogeneic SCTs performed in older patients is increasing, which goes along with an increasing importance of comorbidities in the risk assessment prior to transplantation [39]. Unlike the EBMT registry, the American registry Center for International Blood and Marrow Transplant Research (CIBMTR) contains data on comorbidities. The Loberiza 2005 study included in the report used data from the IBMTR and ABMTR registries, which became part of the CIBMTR when it was established in 2004. However, the risk adjustment in the Loberiza 2005 study did not account for comorbidities either. Since adjustment for comorbidities was not explicitly required by the inclusion criteria and the adjustment was otherwise adequate, the studies were included in the assessment.

Accounting for cluster effects

A critical inclusion criterion of this assessment was the consideration of cluster effects. Some of the studies screened in full text investigated the outcomes on the level of the individual patient and correlated them with characteristics of the hospital or physician. But they failed to take into account the fact that the quality of treatment outcomes for patients who were treated by the same person or in the same hospital is not independent in the same way as it is in patients treated by different physicians or in different hospitals. Disregard of cluster effects leads to overestimates of effects and excessively narrow estimates of confidence intervals [25].

The studies included in the report looked at the transplantation centre or the individual physician as a cluster, but none of the studies considered the cluster effect on multiple levels, namely the physician and transplantation centre level [40].

One study, although important in light of its high patient numbers, but excluded due to ignored cluster effects was the study by Marmor et al. [41]. It investigated the relationship between the

quality of treatment outcome in stem cell transplantation and accreditation of the transplant centre with the U.S. Foundation for the Accreditation of Cellular Therapy (FACT). For this investigation, data from the registry of the statistical centre of the Center for International Blood and Marrow Transplant Research (CIBMTR) were analysed.

Further factors influencing the quality of treatment outcome

In addition to the volume of services, a hospital's structural and staff conditions influence the quality of the treatment outcome. Structural conditions include the spatial, technical, and medical equipment as well as organizational structures. Concerning staffing conditions, distinctions are made between occupational groups of physicians, nurses, etc., as well as between their qualifications and staffing levels [33]. Some of these influencing factors are being discussed below.

Accreditation

Three studies included in this report investigated the influence of transplantation centre accreditation by JACIE, the accreditation system of EBMT and ISCT, on the quality of the treatment outcome. JACIE collaborates with the U.S. accreditation system FACT. Both accreditation systems continuously develop and update standards for the entire transplantation process, from donor/recipient selection to follow-up care, including graft collection, characterization, processing, and storage. In addition, a quality management system is embedded in each individual area. Accreditation requirements include the volume of services of the transplant centre as well as structural and staffing conditions.

In the Loberiza 2005 study, whose results were of high informative value, no influence of FACT accreditation on the quality of treatment outcome was found for either allogeneic or autologous SCT. In 2015, Marmor et al. arrived at the same conclusion in a study which was also based on an American registry (CIBMTR) but was excluded from this report since it ignored cluster effects [41]. Marmor et al. substantiated their result on the grounds that, at the time of the Marmor 2015 study, approximately 90% of all transplantation centres in the USA were FACT-accredited, that patient care in accordance with the FACT accreditation system was widespread and standardized, and that this care was adopted in the Standard Operating Procedures (SOPs) of many transplantation centres, even unaccredited ones.

A different conclusion was reached by the Gratwohl 2015, Gratwohl 2014, and Schetelig 2017 studies, which are based on the European EBMT registry and were included in this report. For allogeneic SCT, they reported that JACIE accreditation of a transplantation centre is associated with significantly higher overall survival or event-free survival. However, the studies' results were of low informative value. For autologous SCT, the transplantation centre accreditation did not significantly influence the quality of treatment outcome in these studies. Gratwohl et al. explain the stronger effect for allogeneic SCT versus autologous SCT by the fact that allogeneic SCT is more complex [42] and regulation through a quality management system thus having a greater influence on the quality of treatment outcomes.

Emergency treatment of complications following transplantation

The challenges in the care of patients with allogeneic SCT are also demonstrated by the following results: The Loberiza 2005 study reported significantly higher overall survival after 100 days for allogeneic SCT using an HLA-identical twin donor if the initial contact outside of office hours or in emergencies was with an experienced physician. This result is explained by the fact that complications during the follow-up period are diagnosed and treated faster in these cases.

For other surgeries, lower overall survival due to insufficient diagnosis and/or treatment of life-threatening complications has likewise been reported for hospitals with a low volume of services versus hospitals with a high volume of services [43–45].

Transplantation centre experience with SCTs

The quality of treatment outcome in SCT further correlates with the transplantation centre's experience with the respective primary disease. In the Gratwohl 2015 study with a low informative value of results, a significant increase in overall survival and relapse-free survival as well as a significant decrease of non-relapse mortality and relapse was shown if allogeneic SCT was performed at a transplantation centre which has been performing transplantations for the specific indication for a longer time period. Similar results were found for autologous SCT, but the result for non-relapse mortality was not statistically significant.

In the Schetelig 2017 study, with a low informative value of results, the authors explained their results with the particular importance of the transplantation centre's disease-specific expertise. In this study, the number of allogeneic SCTs performed at a transplantation centre in CLL patients significantly influenced the quality of treatment outcomes of allogeneic SCT performed for this indication. However, the total number of allogeneic SCTs performed at a transplantation centre did not influence the treatment outcome of allogeneic SCT in CLL. Hence, the decisive factor for the quality of treatment outcome seems to be not the performance of allogeneic SCT, but rather the transplantation centre's experience in the care of patients with this specific, rare indication.

Medical school affiliation of the transplantation centre

For both allogeneic and autologous SCT, the Loberiza 2005 study also found a statistically significantly lower overall survival after 100 days if the transplantation centre was affiliated with a medical school or mentored students or registrars. According to the study's authors, this may be due to (1) inexperienced students and physicians being involved in patient care, (2) physicians who provide patient care and perform teaching activities simultaneously having less time available for actual patient care, and/or (3) patient care being more consistent if performed by trained staff.

Effects of a minimum number of cases being introduced in patient care (research question 2)

No adequately controlled interventional studies were found for answering the question about the effects of a minimum number of cases being introduced in patient care. However, such studies would be necessary in order to draw a sound conclusion and substantiate causality.

The investigation of the effects of a minimum number of cases established in patient care would also require the stringent implementation of minimum volume rules. However, in the German healthcare setting, it was found that minimum volume rules are not met by all hospitals performing SCT. A comparative analysis of 3 consecutive hospital quality reports done for the years 2006, 2008, and 2010 showed that only 57% of hospitals met the minimum volume rules in all 3 reporting years. Minimum volume rules were not met in any reporting year by 16% of hospitals and not met continuously by 27% [46].

The new minimum volume rules coming into effect on 1 January 2018 are expected to facilitate a more stringent implementation of the specified minimum volumes. This is because hospital owners must now annually declare, on the basis of a “reasonable volume expectation”, whether the required minimum volume is likely to be met in the next calendar year. If there is no expectation of such and no exception can be claimed, hospitals are prohibited from rendering the service and are not entitled to reimbursement [8, 47].

Hence, the conditions for conducting studies to answer the important research question 2 are improving, and it remains to be hoped that future studies will investigate the effects of minimum case numbers established in patient care.

7 Conclusion

For the investigation of a correlation between volume of services and quality of treatment outcome in haematopoietic stem cell transplantations, a total of 4 registry studies were eligible for inclusion in the assessment. For 1 study, the informative value of results was rated as high. Among the outcomes relevant for the report, this study investigated only overall survival.

As regards the outcome of overall survival, the results with high informative value show, for both transplantation types, a significant increase with rising volume of services on the level of the treating physician after up to 1 year. This positive correlation between the volume of services and quality of treatment outcome is also shown for a follow-up period of 8 years by studies with low informative value of results; these studies considered the volume of services at the transplantation centre level.

For the other outcomes, only studies with low informative value of results were available. For the combined outcome of event-free survival after allogeneic SCT, a weak positive correlation between volume of services and event-free survival was derived only whenever the volume of services was defined disease-specifically for CLL patients. A weak positive correlation between volume of services and non-relapse mortality after allogeneic SCT can also be derived for a follow-up period of 8 years. For shorter follow-up periods, the observed correlations are even weaker. In addition, a weak positive correlation between volume of services and relapse-free survival was found for allogeneic or autologous SCT as well as between volume of services and occurrence of relapse/progression for autologous SCT. In comparison, the observed correlation between the outcome of occurrence of relapse/progression after 5 or 6 years of follow-up, respectively, was weaker for allogeneic SCT.

No correlation was derived between volume of services and non-relapse mortality in autologous SCT or occurrence of relapse/progression in allogeneic SCT at a follow-up period of 8 years.

The included studies did not provide any usable data or did not report any data on other outcomes, such as acute or chronic GvHD or quality of life.

No studies were found for investigating the effects of specific minimum case numbers implemented in patient care for stem cell transplantation on the quality of treatment outcomes.

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The full report (German version) is published under

https://www.iqwig.de/en/projects-results/projects/health-care/v18-02-relationship-between-volume-of-services-and-quality-of-treatment-outcome-for-stem-cell-transplantation-rapid-report.10146.html

Appendix A – Search strategies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 06, 2018
- Ovid MEDLINE(R) 1946 to November Week 5 2018
- Ovid MEDLINE(R) Daily Update December 06, 2018
- Ovid MEDLINE(R) Epub Ahead of Print December 06, 2018

#	**Searches**
1	Bone Marrow Transplantation/
2	exp Stem Cell Transplantation/
3	(((stem adj1 cell*) or (bone adj1 marrow*) or allogeneic* or autologous* or peripheral blood progenitor cell*) adj3 transplant*).ti,ab.
4	SCT*.ti,ab.
5	or/1-4
6	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
7	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
8	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
9	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj2 (volume* or caseload* or experience* or characteristic*)).ab,ti.
10	((improved adj1 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
11	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
12	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
13	or/6-12
14	and/5,13
15	14 not (exp animals/ not humans.sh.)
16	15 not (comment or editorial).pt.
17	..l/ 16 yr=2000-Current

2. PubMed

Search interface: NLM

- PubMed – as supplied by publisher
- PubMed – in process
- PubMed – pubmednotmedline

Search	Query
#1	Search SCT*[TIAB]
#2	Search "stem cell transplantation" [TIAB] OR "stem cell transplantations" [TIAB] OR "stem cell transplants" [TIAB] OR "stem cell transplant" [TIAB] OR "bone marrow transplantation"[TIAB] OR "bone marrow transplantations"[TIAB] OR "bone marrow transplant"[TIAB] OR "allogeneic transplantation" [TIAB] OR "allogeneic transplant" OR "allogeneic transplantations" [TIAB] OR "allogeneic transplants" [TIAB] OR "autologous transplantation" [TIAB] OR "autologous transplantations" [TIAB] OR "autologous transplant" [TIAB] OR "peripheral blood progenitor cell"[TIAB]
#3	Search #1 OR #2
#4	Search "minimum volume" [TIAB] OR "minimum volumes" [TIAB] OR "caseload" [TIAB] OR "volume outcome" [TIAB] OR "minimal provider volume"[TIAB] OR "patient volume"[TIAB] OR "patient volumes"[TIAB] OR "high volume"[TIAB] OR "higher volume"[TIAB] OR "low volume"[TIAB] OR "lower volume"[TIAB]
#5	Search "hospital factors"[TIAB] OR "hospital factor"[TIAB] OR "centre effect"[TIAB] OR "centre effects"[TIAB] OR "centre factors"[TIAB] OR "center effect"[TIAB] OR "center effects"[TIAB] OR "provider factors"[TIAB] OR "surgeon factors"[TIAB] OR "surgeon related factors"[TIAB]
#6	Search "level center"[TIAB] OR "hospital level"[TIAB] OR "level centres"[TIAB] OR "level hospitals"[TIAB] OR "hospital type"[TIAB] OR "type of hospital"[TIAB] OR "smaller units"[TIAB] OR "smallest units"[TIAB] OR "small units"[TIAB] OR "small unit"[TIAB] OR "smaller hospital"[TIAB] OR "hospital size"[TIAB]
#7	Search "hospital volume"[TIAB] OR "hospital volumes"[TIAB] OR "hospital characteristics"[TIAB] OR "volume hospitals"[TIAB] OR "hospital experience" [TIAB] OR "provider volume"[TIAB] OR "provider volumes"[TIAB]OR "unit volume"[TIAB] OR "surgical volume"[TIAB] OR "surgical experience"[TIAB] OR "units characteristics"[TIAB] OR "unit characteristics"[TIAB] OR "center experience"[TIAB] OR "surgeon volume"[TIAB] OR "physician volume"[TIAB] OR "centre experience"[TIAB] OR "provider characteristics"[TIAB] OR "surgeon characteristics"[TIAB] OR "surgeon experience"[TIAB] OR "volume per surgeon"[TIAB] OR "center volume"[TIAB] OR "physician characteristics"[TIAB]

Search	Query
#8	Search ("improved outcome" [TIAB] OR "improved outcomes" [TIAB]) AND (hospital* [TIAB] OR center[TIAB] OR centers[TIAB] OR centre* [TIAB] OR unit* [TIAB] OR surgeon* [TIAB])
#9	Search "selective referral"[TIAB] OR "volume based referral"[TIAB] OR "selective referrals"[TIAB] OR "referral rates"[TIAB]
#10	Search (surgeon* [TIAB] OR surgical* [TIAB] OR physician* [TIAB] OR provider* [TIAB] OR specialist* [TIAB]) AND outcome* [TIAB]
#11	Search #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	Search #3 AND #11
#13	Search #12 NOT Medline [SB]
#14	Search #13 AND 2000:2018 [DP]

3. Embase

Search interface: Ovid

- Embase 1974 to 2018 December 07

#	Searches
1	exp bone marrow transplantation/
2	exp stem cell transplantation/
3	SCT*.ti,ab.
4	(((stem adj1 cell*) or (bone adj1 marrow*) or allogeneic* or autologous* or peripheral blood progenitor cell*) adj3 transplant*).ti,ab.
5	or/1-4
6	((minim* or high* or low or patient or outcome* or importance*) adj3 (volume* or caseload)).ab,ti.
7	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) adj2 (factor* or effect*)).ab,ti.
8	((hospital* or center* or centre* or unit*) adj5 (type or level or small* or size)).ab,ti.
9	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) adj2 (volume* or caseload* or experience* or characteristic*)).ab,ti.
10	((improved adj1 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)).ti,ab.
11	((surgeon* or surgical* or physician* or provider* or specialist*) adj3 outcome*).ti,ab.
12	(referral* adj3 (selective* or volume* or rate*)).ti,ab.
13	or/6-12
14	and/5,13

#	Searches
15	14 not medline.cr.
16	15 not (exp animal/ not exp human/)
17	16 not (Conference Abstract or Conference Review or Editorial).pt.
18	..l/ 17 yr=2000-Current

4. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 12 of 12, December 2018
- Cochrane Central Register of Controlled Trials: Issue 12 of 12, December 2018

ID	Search
#1	[mh ^"Bone Marrow Transplantation"]
#2	[mh "Stem Cell Transplantation"]
#3	SCT*:ti,ab
#4	(((stem NEAR/1 cell*) or (bone NEAR/1 marrow*) or allogeneic* or autologous* or peripheral blood progenitor cell*) NEAR/3 transplant*):ti,ab
#5	#1 or #2 or #3 or #4
#6	((minim* or high* or low or patient or outcome* or importance*) NEAR/3 (volume* or caseload)):ti,ab
#7	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) NEAR/2 (factor* or effect*)):ti,ab
#8	((hospital* or center* or centre* or unit*) NEAR/5 (type or level or small* or size)):ti,ab
#9	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) NEAR/2 (volume* or caseload* or experience* or characteristic*)):ti,ab
#10	((improved NEAR/1 outcome*) and (hospital* or center* or centre* or unit* or surgeon*)):ti,ab
#11	((surgeon* or surgical* or physician* or provider* or specialist*) NEAR/3 outcome*):ti,ab
#12	(referral* NEAR/3 (selective* or volume* or rate*)):ti,ab
#13	#6 or #7 or #8 or #9 or #10 or #11 or #12
#14	#5 and #13 with Cochrane Library publication date Between Jan 2000 and Dec 2018, in Cochrane Reviews
#15	#5 and #13 with Publication Year from 2000 to 2018, in Trials

5. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	(MeSH DESCRIPTOR Bone Marrow Transplantation)
2	(MeSH DESCRIPTOR Stem Cell Transplantation EXPLODE ALL TREES)
3	(SCT*)
4	(((stem cell* OR bone marrow* OR allogeneic* OR autologous* OR peripheral blood progenitor cell*) NEAR3 transplant*))
5	#1 OR #2 OR #3 OR #4
6	((minim* or high* or low or patient or outcome* or importance*) NEAR3 (volume* or caseload))
7	((hospital* or center* or centre* or unit* or surgeon* or provider* or physician*) NEAR2 (factor* or effect*))
8	((hospital* or center* or centre* or unit*) NEAR5 (type or level or small* or size))
9	((hospital* or center* or centre* or unit* or surgeon* or surgical* or physician* or provider*) NEAR2 (volume* or caseload* or experience* or characteristic*))
10	((improved NEAR1 outcome*) AND (hospital* or center* or centre* or unit* or surgeon*))
11	((surgeon* or surgical* or physician* or provider* or specialist*) NEAR3 outcome*)
12	(referral* NEAR3 (selective* or volume* or rate*))
13	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14	#5 AND #13
15	(#14) FROM 2000 TO 2018
16	(#15) IN HTA FROM 2000 TO 2018