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Determining an indicator list for benchmarking delivery logistics in proton therapy treatment

And a systematic review of operations research application in particle therapy logistics

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Abstract

Introduction: The application of particle therapy (PT) for treatment of cancer patients is increasing worldwide. PT centres can easily cost in excess of €100M to build and operate and should therefore be operated as efficiently as possible. Operations research (OR) is a field of mathematics that is applied to optimise processes. Benchmarking is a method used to compare processes and identify areas of improvement for benchmarking partners. The goal of the paper is to create a list of viable data indicators for a benchmark study and supply an overview of current OR methods used in PT to guide future improvement.

Methods: A benchmarking system for specialty hospitals was applied to PT centres. Stakeholder and PT process analysis were used to construct a list of indicators to be assessed by PT centres for data availability, definition clarity, and discriminative value. The results of the assessment were used to determine viable indicators. Additionally, PubMed and Scopus were searched for papers on OR application in PT treatment logistics. Databases were searched from 2000 to February 2016. Inclusion criteria were presence of OR methods and application of these methods in the treatment phase of PT.

Results: From the original list of 28 proposed indicators, eight were approved, six were conditionally approved, two were merged, three were modified, and nine were discarded. From the literature review, another two indicators were added. Nine studies were included in the literature review: The literature search returned 42 results from which five papers were included in the study. Four additional papers were included from references.

Conclusion: PT centres gather enough data for a viable comparison in a benchmark but extraction of large amounts of data can be troublesome . Users of the indicator list should take care to correct for differences in data entry points. Literature review shows that simulation and linear programming are the most applied OR methods in PT. Radiation delivery processes are well modelled but staff utilisation is not.

Key Words: Proton therapy, Operations Research, Benchmarking, Stakeholder analysis, Indicator, Systematic Review.

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1. Introduction

The use of particle therapy (PT), such as protons and carbon ions, for cancer treatment is expanding rapidly and being implemented on a worldwide scale. Although the therapeutic possibilities of proton particle beams have been long known (1, 2) and facilities providing such treatment have been in operation at research institutes since 1969 (3), technological and medical advances have allowed the construction of specialised multi-room hospital based particle therapy centres on an increasing scale since 1990 and especially since the start of the 21st century. (2-5) Currently, there are over thirty facilities in operation which have treated over 100.000 patients as of December 2013. (6) Another 44 are under construction or in the planning stage, four of which are in The Netherlands. (7, 8)

Porter defines value in healthcare as *outcomes / costs*. (9) Proton beam therapy has been proven to reduce the risk of damage to surrounding tissue for selected indications while achieving same or better tumour control, leading to better health outcomes and a reduced risk of side-effects. The cost-effectiveness of proton therapy compared to state-of-the-art photon therapy such as IMRT is, due to high initial investment costs and the current lack of high-quality comparisons of clinical outcomes, at best disputed. (5, 10-13) While clinical trials to investigate the effect on medical outcomes are part of regular operations in most PT centres, it is less common to research the operational practices of PT centres regarding the other aspects of the value equation: costs, and non-medical outcomes such as patient and staff satisfaction.

Operations management (OM) is a combination of operations research and management science (OR/MS) methods that can be applied to analyse and improve production processes. OR quantitative methods are especially applicable to logistics and planning processes, which are important to improve the use of resources while accounting for user preferences. (14) For further effect, operations research can be combined with business quality management practices like LEAN and Six Sigma to reduce and prevent waste and reduce variance in healthcare operations. (15-17)

Operations research is widely used in healthcare settings to optimise processes: Hulshof et al. (18) have determined that five basic OR/MS methods can be applied to optimising the design of ambulatory care healthcare delivery: Computer simulation, heuristics, Markov processes, queueing processes and mathematical programming. In the specific case of cancer treatment, studies have been conducted which have shown that mathematical programming and computer simulation of processes can be applied to, for instance, reduce access time, variance of access time and linear accelerator planning (19-22) and optimise radiotherapeutic dose delivery (23). However, most of these studies concern radiotherapy, not particle therapy, and no systematic review of operations management studies in proton therapy logistics has been published to date.

Benchmarking is an OM method that can be used to compare operations and identify best practices. (24) Van Lent, De Beer & Van Harten have developed a framework for benchmarking specialty hospitals, including cancer therapy centres. (16) Objective and comparable data indicators are critical elements of a benchmark process. As to date, no indicator set has been developed for PT, a benchmark of existing PT centres cannot yet be performed. A study of current practices and present research is required to develop such an indicator set.

A combined study of indicator set development, including adjudication by operational centres, and a systematic literature search reviewing present literature on OM practices in PT logistics has been performed to achieve the following objectives:

1. To determine a feasible set of data indicators to be used in a benchmark of proton therapy centres,
2. To determine the current state of operations research in proton therapy logistics and how this research compares, especially regarding the indicators used, to the operational demands of active proton therapy centres, and:
3. Identification of opportunities for improvement in operating proton therapy facilities, primarily (but not limited to) using operations research methods.

2. Research methods

Two separate methods are required to give a complete overview of the available information. First, the benchmark protocol by Van Lent, De Beer & Van Harten (16) was used to investigate available information (data indicators) that can be used to perform a future benchmark. Second, a systematic literature review was performed to determine the current state of OR applications in PT, to identify the OR methods, objectives, and indicators used, and to identify differences between these studies and the operational feedback from benchmark participants.

Feedback from the participating centres on the availability of data and the questionnaire regarding priorities and working methods has been used to compile a list of accepted indicators. This list of indicators has been compared to the indicators found in the literature search to identify and add indicators missing from the vetted list that are of importance to OR research. Last, both areas where current models can be expanded using available data and areas of interest that no current model covers are assessed for future research.

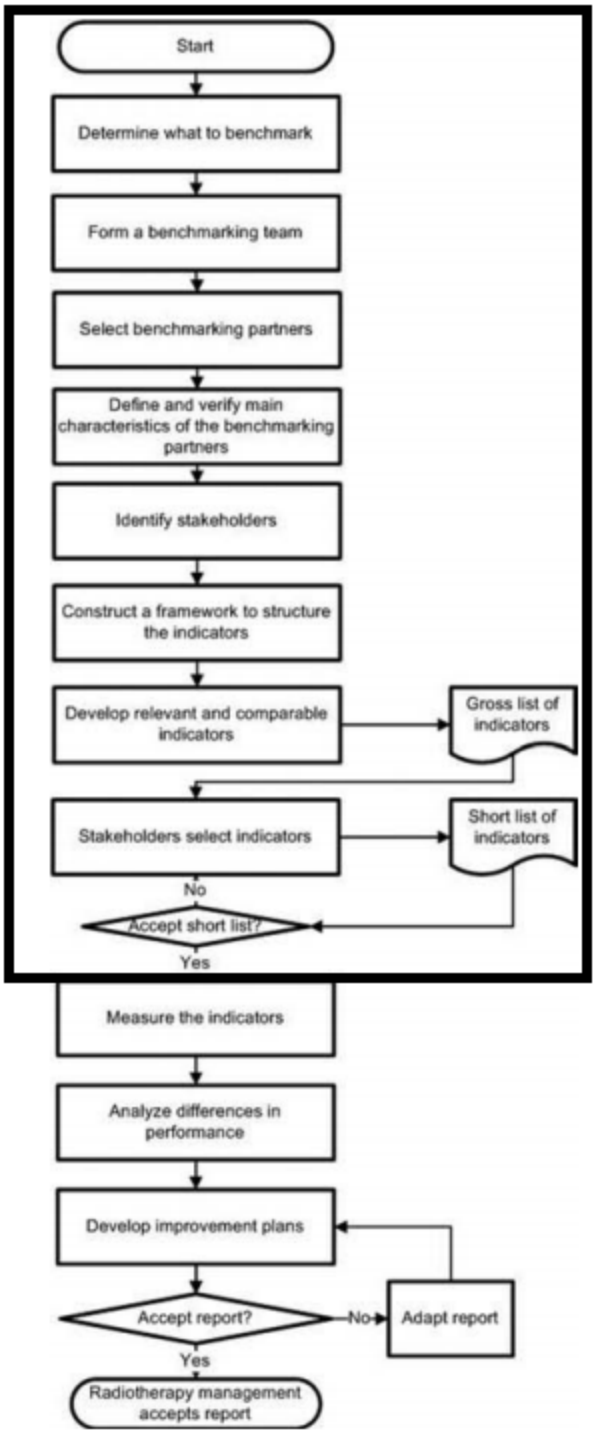

Figure 1: "Benchmarking process, visual representation of the research method". **First published by Van Lent, de Beer, van Triest & van Harten (24), box added to denote study scope**

2.1 Benchmark indicator selection

The benchmark protocol (16) is designed for international benchmarking of specialty hospitals. Specialty hospitals have been described by Schneider et al. (25) as hospitals "that treat patients with specific medical conditions or those in need of specific medical or surgical procedures." Proton therapy centres, due to their singular focus on cancer treatment, fit very well within this categorization. Therefore, this method is suitable for the intended benchmark.

This study focuses on the development of an indicator list for a future benchmark. The following steps from this method have been executed in this study:

- Determining benchmark scope
- Selection, definition and verification of main characteristics of benchmarking partners.
- Identification of relevant stakeholders.
- Defining benchmarking domains and indicators.
- Obtaining stakeholder input and feedback on indicators, domains and framework

The benchmarking process itself has been visualised by Van Lent, de Beer, van Triest & van Harten in figure 1 (26), The scope of the indicator selection process is shown within the black rectangle.

2.1.1 Determining benchmark scope

Scientific papers on particle therapy processes (4, 27-31), PT centre websites (32-34) and other sources (35, 36) were consulted to get an overview of the workings of a particle therapy facility. Although more detailed medical and technical information is available on every step of the PT process, a general overview suffices to construct the workflow of a PT centre and differentiate relevant indicators.

Particle therapy treatment processes consist of two distinct phases: 1) the pre-treatment phase, consisting of intake, (additional) diagnosis and treatment /dose planning, and 2) the treatment phase, which concerns the actual delivery of the dose by a particle accelerator and is split up into several fractions (visits). (4, 19) A purely logistical benchmark will be limited to the treatment phase: although the pre-treatment phase can be measured and compared, the efficiency of this process is not crucial to the efficiency of the treatment phase. The configuration of particle accelerator and treatment rooms are the primary strategic factor in determining the capacity of a PT centre and are set by the way the centre is constructed. This configuration cannot be changed on an operational level as changes would require costly additional construction and are very disruptive to operational processes. Diagnostics capacity in the pre-treatment phase, imaging capacity in the treatment phase and required staff in both phases can be changed more easily by hiring more staff and construction of diagnostics/imaging capacity is less expensive or disruptive than treatment rooms. Most of the activities in the pre-treatment phase are started some 7-10 days in advance but can be completed in a shorter period if necessary. The availability of a first appointment slot in the treatment phase is the determining factor in the required completion time of this phase.

Limiting the scope of the benchmark to the treatment phase will also limit the number of indicators required and the associated resources for collection and analysis. Therefore, the treatment delivery phase in general and specifically the use of the particle accelerator is the primary focus of this study and we start analysing the process from the moment a complete treatment plan has been generated and is ready for independent verification. The final point of the scope is the end of the treatment process, i.e. when the final fraction has been delivered. A schematic overview of which parts of the proton therapy process are covered by this study can be found in figure 2.

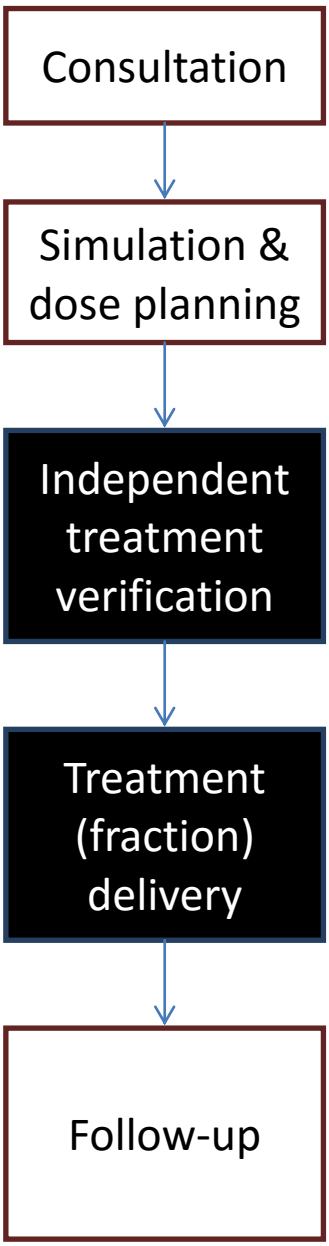

Figure 2: Parts of proton therapy process included in study**. black = included, white = not included.**

2.1.2 Benchmark partner selection

While the benchmark in general focuses on the entire range of patients in a PT centre, it may be unlikely that a PT centre treats all different tumour types in sufficient numbers to generate enough evidence suitable for comparison. Therefore, the patient scope of the study focuses on specific tumour categories in both adult and paediatric patients as noted in Table 1. These tumour categories have been

selected to reflect the most important and likely categories of patients for proton therapy: in Italy (37), the Netherlands (38) and the U.K. (39) these categories are included in the standard indications for proton therapy, meaning that these are tumour types to be primarily treated with protons. Within these standard indications these are the most complex tumour types, often requiring multiple angles of irradiation, and therefore the most likely to benefit from OR optimisation. Participating centres can take part in either the benchmark of adult patient processes, the paediatric benchmark or both.

Table 1: Patient categories for analysis

Patient category	**Process type**
Adult	Skull base tumours (40-43)
	Tumours of the head and neck (44-47)
Paediatric (anaesthesia)	Medulloblastoma (48, 49)
	Ependymoma (49, 50)

For the benchmark of treatment processes for adults, participating centres have to meet the following characteristics: 1) centres have treated or are planning to treat skull base and/or head and neck tumours and have in place or designed logistical (not clinical) processes for treatment of said tumours, and 2) deliver treatment using a pencil-beam (spot)-scanning or IMPT system.

Centres in the paediatric benchmark will have to treat or intend to treat significant numbers of paediatric Medulloblastoma and Ependymoma under anaesthesia. Because of the relatively low incidence of paediatric cancers and the relatively high amount of time associated with anaesthesia compared to the treatment delivery, neither the type of treatment delivery technique used nor the location where anaesthesia is administered is of concern in the paediatric benchmark.

2.1.3 Stakeholder analysis

Stakeholder identification has started with the research performed by Van Lent, De Beer & Van Harten (16), who have identified cancer centre management, radiotherapy department management, radiation oncologists and clinical physicists as stakeholders. Further identification was performed by analysing PT delivery for the presence of stakeholders within the classification used by Patel et al. and grouped accordingly. (51)

Present stakeholders have been analysed using the framework of Mitchell, Agle & Wood. (52) The authors define stakeholders in terms of possession of three attributes: power, legitimacy, and urgency, described in Table 2. Stakeholders are placed in eight different categories, dependent on possessing

one or more of these attributes. Only stakeholders that possess all three attributes, termed “definitive stakeholders”, will be included in the indicator selection.

Table 2: Stakeholder attributes according to Mitchell, Agle & Wood

Attribute	**Description** (original from Mitchell, Agle & Wood, 1997: table 3, p.869) (52))
Power	“A relationship among social actors in which one social actor, A, can get another social actor, B, to do something that B would not have otherwise done.“
Legitimacy	"A generalized perception or assumption that the actions of an entity are desirable, proper, or appropriate within some socially constructed system of norms, values, beliefs, and definitions"
Urgency	“The degree to which stakeholder claims call for immediate attention.”

Within the operational scope of this benchmark, Power can be explained as the ability to immediately influence, disrupt or change logistical procedures, legitimacy as a genuine claim to consideration in the day to day details of treatment delivery and urgency as the degree in which a stakeholder should be consulted on a frequent basis. As can be seen in Table 3, healthcare professionals involved in the day to day operations of the clinic are all definitive stakeholders, as they have direct control over these processes, and are included in the indicator selection.

Table 3: Stakeholder analysis

Stakeholder	**Power**	**Legitimacy**	**Urgency**	**Category**
Healthcare professionals				
- Management	+	+	+	Definitive
- Oncologist	+	+	+	Definitive
- Physicist / Technician	+	+	+	Definitive
- Nursing staff	+	+	+	Definitive
Patient & support				
- Patient	-	+	+	Dependent
- Family/caregivers	-	+	-	Discretionary
- Referring Physician	-	-	-	None
Payer groups				
- Insurance	+	-	+	Dangerous
- Financiers	+	-	-	Dormant
Healthcare delivery system				
- Government	+	+	-	Dominant
- Parent hospital system	+	+	-	Dominant

Mitchell, Agle & Wood (52) discuss the possibility stakeholders can gain or lose attributes and the associated relevance. This is most important when a stakeholder possesses two out of three attributes, in this case patients, insurers, government and the parent hospital system. Patient's needs are normally managed by the centre's staff, in terms of access time, appointment slots and medical effectiveness, and patients have little individual power over the procedures. However, when a patients' needs are not carefully monitored or in case of complications, patients can gain power, for instance by utilising insurers, patient organisations or the media to draw attention. Insurance companies are not normally inclined nor expected to interfere with the day to day proceedings of medical institutions but can gain legitimacy if their demands, for instance access time and costs, are not met by the centre. The power of insurers to move business is considerable. The government and parent hospital do not normally have an urgent claim to interference on an operational level but can become powerful stakeholders in case of underperformance or changes in the way these institutions conduct business, such as reorganisations or changes in healthcare laws, as centres are dependent on the frameworks set by these stakeholders.

Stakeholders who possess only two out of three attributes may not have a significant influence on day to day operations, but their objectives must not be ignored in any change process. To simplify the indicator approval process, we have assumed that the patients interest are championed by the doctors in reducing access and throughput times, the institutional stakeholders (government, insurer, parent system) are taken care of by management and that physicists and technical staff, due to their overlapping responsibilities, can be combined into one category.

2.1.4 Defining benchmarking framework, domains and indicators.

The benchmark framework consists of two different analyses: qualitative analysis and quantitative analysis. The qualitative analysis concerns the comparison and evaluation of the design of logistical (non-medical) protocols in use at a centre to identify differences in the way a centre handles patients, resources and information streams required to facilitate particle therapy treatment. Since this is an evaluation of design, this can also be done in centres that are not yet in operation. The quantitative analysis concerns the performance of the designed logistical protocols and is being done through the measurement of key performance indicators throughout the process. When a difference in performance is measured, design analysis can be used to account for the difference and define areas of improvement for centres where performance is not optimal.

Qualitative analysis

For the analysis of process design both process descriptions and information on the framework, resources, and strategy used in a centre are required. Flowcharts are a common way to map processes and identify relevant points for measurement and indicator selection. (53) Flowcharts can be standardised in a way that shows common activities at the same point in a chart, which is useful to determine the number of activities centres employ to reach certain points in their process and any differences between participating centres.

The benchmark requires general descriptions for processes for both adult and paediatric patients and, when different from the general process, more in-depth information about the selected patient categories in Table 1. Information is needed concerning four different logistical processes: the patient process, which concerns activities of the patient, the administrative process, which concerns information transfers required to treat the patient, the technological process**,** which concerns the preparation and use of the proton beam treatment rooms, and the medical professional process which concerns staff planning and availability. These processes will largely coincide, as the activities in one process are entangled with the three other processes, and can therefore be graphically combined in key stages of the treatment delivery. This will give a clear overview of the preparations and executions in each centre. An overview of information required for constructing the process maps can be found in Table 4.

Table 4: Information required for construction of process flowcharts

1. Name of process step (for instance immobilisation)
2. Resources and materials required (i.e. mask, gantry) → technological process
3. Staff required → professional process
4. Patient required? → patient process
5. Information required → administrative process
6. Physical space (room) required
7. Processes required being complete before start.
8. General indication of time required to complete step (expert opinion)

Furthermore, information is needed because differences in operating procedures outside the direct logistical process may influence the results of the quantitative measurements. It is necessary to have additional information about resource use, operating framework and staffing levels of centres to determine the baseline levels in which a centre operates and to determine how to correct for differences within these baselines.

The stakeholder analysis has been used to assemble a questionnaire which covers the domains of the respective stakeholders. Management domains include operating hours and days, patient mix, insurance approval, staff and patient satisfaction and service levels. Medical staff domains concern

access time, service quality, shared decision making and patient satisfaction. Technical aspects are limited to the required maintenance and associated loss of operating time.

Additional questions are included concerning the appointment scheduling process used in the centres. Successful utilisation of a shared resource, such as particle accelerators and gantries can be seen as a combination of two factors: appointment scheduling and the execution of this schedule. (54) There are two distinct steps in the scheduling process for which information is required: tactical block scheduling, which allocates treatment time in large blocks for a period of months, operational treatment appointment planning that distributes the allocated blocks over specific patients. Last, information on the treatment planning verification procedure is needed to assess the procedure to approve a patient for the start of the irradiation.

A complete overview of the questions can be found in Appendix 1.

Quantitative Analysis

In addition to the literature used to determine the benchmark scope processes (4, 27-36), research by Li & Benton (14), Hulshof et al. (18) and Van Lent et al. (26) has been consulted to construct a framework of potential indicators. Li & Benton have defined both production efficiency and utilisation as the main cost performance domains. Hulshof et al. classify radiation as an ambulatory care service and have identified indicators and methods in these fields. Van Lent et al. have performed a benchmark of radiotherapy centres and have established a shortlist of 33 indicators applicable to this cause. Furthermore, a literature search has been performed in the ORCHESTRA (55) database to identify indicators in use in operations research not mentioned in these papers. While the database did not show any papers regarding PT applications of OR, it did give an overview of the data indicator requirements for OR application.

An example of this can be found in a paper by Kortbeek et al. (54), which includes various indicators that are of impact to the performance of a schedule and as such the production efficiency and utilisation. Relevant indicators include the number of resources, time slots length and availability, no shows and access time. Using the information on PT processes, these indicators have been adapted for the PT situation. This paper also indicates the importance of appointment duration, it is relevant to determine the contents of an appointment and influencing factors in some detail. Studies and process descriptions by Combs et al. (4), Rieken et al. (56) and the University of Florida PTC (35) show the process inside the treatment room and give information about the specific steps involved in proton beam delivery. This information has been used in the resource utilisation indicators.

Indicators are divided by Mainz (57, 58), based on Donabedian (59), in structure, process, and outcome indicators. Both structure and process indicators concern the daily operations and are included in this study. (Medical) outcomes are not considered in this study. A list of 46 indicators has

been established as a result of the literature study. Subsequent consultation with Amsterdam Proton Therapy Centre staff with knowledge about the process has reduced the number of indicators for consideration by stakeholders to 28. This list is presented in Appendix 2.

Variance is essential to identify OR research projects, and raw data should be supplied wherever possible. For instance, the numerator time required for treatment plan verification (indicator #7) consists of the added up individual times of treatment verification. These individual times can be used to calculate variance. Indicators are written as if one year of raw data is available.

Structure indicators

Structure indicators concern the proton therapy centre as a whole. All operations in the centre should be considered in determining these indicators.

Staff workload (#1) is a general indicator which can be used to assess differences in staff utilisation. Workload can be defined as the staff-to-patient ratio: the amount of full-time-equivalent (FTE) of staff per patient. As patients require different amounts of fractions, it is more useful to use fractions as the denominator. Patient population (#2-3) concerns the amount and type of patients that are (expected to be) treated at a centre to get an overview of the case mix per centre. These indicators concern the entire patient population of a participating centre and are required to properly scale activities and resources for comparison. Data for these indicators is also used in many process indicators. Available equipment (#4,5,6) should be assessed to calculate utilisation and correct for differences between centres.

Process indicators

Process indicators are not automatically homogenous for a facility as a whole. Therefore, when the indicator requires patient-specific information for the nominator or denominator (such as the number of fractions), indicators should be stratified per tumour type to generate comparable results. The ideal situation would be to have as much data on different tumour types as possible, but the minimum requirement would be information on the patients types as determined in Table 1.

In all stages, access and throughput time (#7-12) is crucial from a patient's perspective: a loss of time has been shown to negatively affect the outcomes of the treatment process. (60-62) Patient punctuality(#13-16) plays a main role in the treatment process. Patient waiting times are essential to a good schedule: waiting time should be minimised, but patients should arrive in time for the planned appointment. Staff productivity (#17) concerns the availability of staff to execute the treatment. Resource utilisation (#17-25) concerns the use of (technological) resources, in this case the particle accelerator and treatment rooms. Resource use indicators have been divided in primary indicators (#17,18,19), which are essential to the benchmark and calculate the throughput time of the entire irradiation process, and secondary indicators (#20-24) that split the primary activity in more detailed steps, which are not essential but may prove interesting when data is easily available. Downtime (#26-

28) should be minimised for efficient operations but cannot be totally avoided. This section provides indicators for downtime and maintenance measurement. In this case, working hours are hours that a patient normally could have been treated. Quality assurance is required to assure correct targeting precision to make sure the beam is delivered to the specification of the treatment plan.

2.1.5 Stakeholder assessment of indicators

Centres were asked to have at least one senior representative from each stakeholder group and a data specialist (for instance scheduling programme key user) give their opinion on the questions asked in the questionnaire and adjudicate indicators on three items: 1) definition clarity, 2) data availability and data reliability and 3) discriminative value. Indicators can be approved, proposed to be adjusted or denied. Feedback was also asked on any missing indicators that centres think are relevant to the benchmark. Last, centres were asked to indicate possible data entry points for the proposed indicators to have an efficient and effective quantitative data collection.

2.2 Systematic literature review

A systematic literature search was performed in Pubmed and Scopus from January 2000 up and until the date of the last search, February 27, 2016. Inclusion criteria were:

1. Item was published in journal, conference proceeding or PhD-thesis
2. Item covers particle therapy,
3. Item describes the application of at least one OR/OM method.
4. Item covers treatment delivery logistics. Most importantly, papers that cover OR/OM methods only to optimise dose delivery, which is outside the scope of the proposed benchmark, were excluded.

To find articles relating to OR/OM research in particle therapy, two search queries were used. First, a direct search was performed for OR/OM in particle therapy. Search terms were placed within brackets as the individual keywords have other meanings within medical research and would return results outside the intended scope.

1: ("Operations research" OR "operations management") AND ("proton therapy" OR "particle therapy" OR "hadron therapy")

OR/OM might not be specifically designated in an article but such articles can contain information on logistical optimisation. Therefore, an additional search was performed on the most common subjects in logistics and capacity planning:

2: (capacity OR throughput OR appointment) AND (planning OR scheduling) AND ("proton therapy" OR "particle therapy" OR "hadron therapy")

References within included articles were screened and articles were sought that cited included articles for additional publications that are relevant to this study.

Articles included were assessed for OR method applied, indicators used and results of the study and described in summary form.

3. Results

3.1 Benchmark indicator selection

The proposed set of indicators and the qualitative questionnaire was sent to eight particle therapy centres: five in Europe and three in the USA. Four European and one US centre (62.5%) have responded and stated their intention to participate in the benchmark process and provide feedback. Two US centres (25%) have indicated that no resources were available to participate and one European centre (12.5%) has not responded.

Formal feedback was received from 5 centres. Feedback on the quantitative indicator set was received from four centres (80%): One centre (20%) was not yet operational and indicated that feedback on the quantitative indicators could not be supplied. Centres were invited to comment on the qualitative indicators as well: one centre (20%) has submitted formal feedback and two other centres (40%) have provided informal feedback during a visit by the author. One centre (20%) indicated that paediatric patients under anaesthesia were rarely treated (~1/year) and that no information could be given on the paediatric procedure. Centres were asked to assess indicators by at least one member of all stakeholder groups but the feedback was received as one document, and the internal assessment procedure is unknown. During site visits to several centres, the author spoke to all stakeholders, except nursing staff, while presenting and discussing the project. A summary of feedback is presented in Table 5, and the assessment of indicators can be found in Table 6

A general remark from all centres concerns the sources of data collection from which indicator data is stored. Raw data of large time periods (>1 year) is preferred for statistical analysis of processes, but there is a large variation between different centres concerning the ease of data extraction and the way information is stored. The required information is stored in several systems such as oncological patient management software, appointment scheduling programmes and proton beam control system logs. While several centres use the same patient management software, for instance Mosaiq (63), not all centres have equal ease of extracting indicator data. Centres differ in the availability of management reporting dashboard extensions that automatically extract data, staff training in the use of the software and the number of departments that have access to the required data.

Table 5: Summary of indicator feedback

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These differences have the greatest effect on indicators that require the number of fractions. One centre has indicated that they have no methods in place to extract the number of fractions for individual patients without extensive amounts of work as data needs to be extracted for individual patients without the option to aggregate data before extraction. The amount of data that centres are willing to provide would be reduced due to the linear scaling of resources required to extract data on patient level: more information would require more staff time and associated expenses. This leads to the conditional approval of indicators #1, #2 and #3: before the benchmark can be performed possibilities to make extraction of patient treatment characteristics, such as scripts used by other centres or other possibilities to initiate a system dump from Mosaiq, should be researched. Alternatively, data collection from this centre could be restricted to the categories mentioned in Table 1 or a period that is representative for the centres activities could be sampled. Other centres have not indicated any problems with the availability of this data. Possible effects of these restrictions will be illustrated in the discussion section.

The way cancer type distribution was described in indicator #2-5 was not clear to all centres. After inquiry as to which classification for tumour type was the most accessible for centres, the use of the ICD-10 classification for patients is the best option to determine tumour type.

Table 6: results of indicator assessment

Title	**Definition Clarity**	**Data availability & reliability**	**Discriminative value**	**Result**
1.Staff workload	+	+/-	+	conditional approve
2.Cancer type distribution	+/-	+/-	+	conditional approve
3.Average fractions per patient per tumour type	+/-	+/-	+	conditional approve
4.Type and number of proton beam treatment rooms	+/-	+	+	approve
5.Tumour type capacity per treatment room	+/-	+	+	approve
6.Facility use outside of treatment stations	+	+	+	approve
7.Time required for treatment plan verification	+/-	+/-	+/-	modify
8.Revision after treatment verification	+	-	-	discard
9.Time required for revision	+	-	-	discard
10.Treatment access time	+	+/-	+/-	modify
11.Time between fractions	+	+	-	discard

12.Treatment completion time	+	+	-	discard
13.Patient on-site waiting time	+	-	-	discard
14.No-shows	+	+	+	approve
15.Patient lateness	+	-	-	discard
16.Staff overtime	+/-	+/-	+	modify
17.appointment duration	+	+	+	approve
18.Radiation time as part of appointment time	+	+	+	approve
19.Proton beam not on patient	+	+	+	approve
20.Proton beam unavailability	+	+	+	approve
21.Treatment room utilisation (immobilisation)	+	+/-	+	conditional approve
22.Treatment room utilisation (positioning)	+	+/-	+	conditional approve
23.Positioning accuracy	+	-	-	discard
24.Treatment room utilisation (nozzle adjustment)	+	-	+	discard
25.Time required for anaesthesia	+	+/-	+	conditional approve
26.Unscheduled maintenance	+	+/-	+	Merge with #27
27.Other downtime	+	+/-	+	Merge with #26
28.Quality assurance time	+	-	-	discard

The time required for treatment plan verification (#7) is structured differently from the way the indicator was proposed. The original indicator was structured from a push-production perspective: treatment can start when the treatment plan is complete and access time of the treatment is the time between completion of the treatment plan and the first appointment. However, in practice centres give the patient starting date immediately at the intake or first imaging appointment based on the centres estimation of the required planning time. The treatment plan needs to be complete at any time before the first treatment appointment, and there is not necessarily a waiting time between these steps. Although the information from the original indicator is available, it is neither reliable nor discriminative to measure access time. It can, however, be used to measure the workload on the physics and planning department. Indicator #7 can be modified to such an extent that when the planning is done and has to be revised, the amount of time left before the start of treatment can indicate whether the department has sufficient time and capacity for revision. This would be quantified as the time between the completion of the planned tumour volume (PTV1, end of planning) and the

time verification by the physics department is complete. The resulting time between the completion of verification and start of treatment can be used to measure the workload of the verification department in indicator #10. While these indicators can only be used to benchmark centres if the expected amount of time left is equal to other centres, it can be valuable for benchmarking against the internal norms of a centre. On indicators #8 and #9, centres have stated that the number of revisions and associated resource spending is not tracked.

Indicators #11 and #12 are discarded due to the way a PT treatment is divided into fractions: all centres have indicated that patients are treated with one fraction per day, five days per week from the start until the completion of the dose requirements. This means that a patient with X fractions requires X days of treatment, and this does not differ between centres. Hypofractionation, the use of a higher dose per fraction in fewer fractions per treatment, is not systematically applied within the responding PT centres. Possible future changes concerning hypofractionation will be discussed later in this paper.

Patient on-site waiting time (#13) and Patient lateness (#15) are not reliably measured by centres. The staff can shift appointments in case of serious disruptions to the schedule. This means that these two indicators are not discriminative for the process as patients can get shifted at the staff's discretion.

Data on staff overtime (#16) is not available for all staff types. Centres have indicated that data is available with regards to the scheduled and realised end of treatment and thus for staff directly involved with the patient process, but not with regards to the support staff and the activities employed after regular treatment hours. The indicator can be modified to measure regular operating overtime only by measuring the difference between the scheduled and realised end time of the last patient.

Data regarding the use of the proton beam (#17-20) is available from logs collected by the accelerator manufacturer for quality and safety purposes. Different manufacturers may use different time stamps for these indicators, an example of possible time stamps for proton beam systems constructed by IBA (64) can be found in Table 7. One centre has replied that indicators #21 and #22 are not measured separately. Information on the total time of these indicators is still usable as the different times can be sampled by individual real-time (stopwatch) measurement but are less representative than a situation in which there is a log time of positioning start. No responding centre uses a positioning system located outside the treatment room. Position accuracy measurements (#23) are not available and this data is largely determined by the quality framework determined by the centre and the intended accuracy levels. Questions regarding this indicator will be moved to the qualitative section. Data on indicator #24 is not available.

Table 7: data entry points for IBA system logs

Indicator	Numerator	Data points
17.	Number of minutes planned in treatment room, per patient, per tumour type.	Time all fields complete – time previous patient all fields complete
18.	Number of minutes of beam in chamber per patient, per tumour type	Time all fields complete – time positioning complete
19.	Number of minutes beam not on patient per year (=number of minutes beam available– numerator of #18)	Time field finished – time field start.
20.	Number of minutes of waiting time due to beam unavailable while patient ready, per tumour type per year	Time field start – time beam requested

Data on unscheduled downtime and maintenance (#26-27) is available in limited form: Not all delays are registered as unscheduled downtime, and the distinction whether unscheduled downtime includes aspects that can be described as maintenance is not clear. One centre has replied that downtime greater than ten minutes is registered in logs but less than ten minutes is not. Therefore, these two indicators can best be combined to include both downtime and maintenance over ten minutes in time. Centres have indicated that quality assurance (QA) occurs outside regular operating hours and is part of the start-up procedure. As with indicator #23, time spent is dependent on the quality and safety framework of the centre and is influenced by the manufacturer and regulatory demands and procedures. It is unlikely that this indicator has discriminative value in an international benchmark.

From the original list of 28 proposed indicators, eight were approved, six were conditionally approved, two were merged, three were modified, and nine were discarded. From the literature review, another two indicators were added. The final list of approved, added, modified and merged indicators can be found in Table 8.

Table 8: final list of indicators

#	Title	*numerator*	*denominator*
Structure I	Staff workload	# Staff (preferably per staff type: oncologist, physicist, nurse, technician etc.) in FTE.	Number of fractions per year (number of patients per ICD-10 category * average number of fractions per type)
II	Cancer type distribution	Number of fractions per ICD-10 category per year	Total amount of fractions per year.
III	Average fractions per patient per tumour type	Number of fractions per ICD-10 category per year	Number of patients per ICD-10 category per year
IV	Type and number of proton beam treatment rooms	Number of (IMPT) gantries, number of horizontal beams etc.	Number of fractions per year (number of patients per ICD-10 category * average number of fractions per type)
V	Tumour type capacity per treatment room	Number of ICD-10 categories treated in centre that can be treated in a particular room (gantry, horizontal beam etc.)	Total number of ICD-10 categories treated in centre.
VI	Facility use outside of treatment stations	number of anaesthetic rooms	Total number of fractions requiring anaesthesia per year.
Verification VII	Time required for treatment plan verification	Time between PTV1 complete and physics verification complete, per ICD-10 category	Number of patients per ICD-10 category
VIII	Time between verification and start of treatment	Total time between physics planning verification complete and first fraction appointment, per patient, per ICD-10 category	Number of patients per year per ICD-10 category

No-shows IX	No-shows	Total number of fractions not delivered due to patient not available, per ICD-10 category	Number of fractions per year, per ICD-10 category
staff X	Staff overtime	Number of minutes worked after scheduled end of last patient treatment, per staff type per year.	Number of working days per year.
throughput XI	Appointment duration	Number of minutes planned in treatment room, per patient, per ICD-10 category	Number of fractions planned per patient, per ICD-10 category
XII	Radiation time as part of appointment time	Number of minutes of beam in chamber per patient, per ICD-10 category	Number of minutes treatment room allocated, per patient, per ICD-10 category
XIII	Proton beam not on patient	Number of minutes beam not on patient per year (=number of minutes beam available– numerator of #18)	Number of minutes beam available for treatment per year
XIV	Proton beam unavailability	Number of minutes of waiting time due to beam unavailable while patient ready, per ICD-10 category per year	Number of minutes of radiation time (including waiting time) per ICD-10 category per year
XV	Treatment room utilisation (immobilisation)	Number of minutes required for immobilisation, per patient per tumour type	Number of minutes treatment room allocated, per patient, per tumour type
XVI	Treatment room utilisation (positioning)	Number of minutes required for positioning, per patient, per ICD-10 category	Number of minutes treatment room allocated, per patient, per ICD-10 category

XVII	Time required for anaesthesia	Number of minutes required for anaesthesia, per patient, per ICD-10 category	Number of fractions, per patient, per ICD-10 category
XVIII	Beam switch time	time field started - time beam requested	Number of minutes treatment room allocated, per patient, per tumour type
XIX	Time per field	time field finished - time field started	Number of minutes treatment room allocated, per patient, per tumour type
downtime XX	Unscheduled maintenance & downtime	Number of minutes of unscheduled delay >10 minutes during working hours, per year.	Number of minutes within working hours, per year

3.2 Qualitative questionnaire

Assessment of the qualitative questionnaire showed that two areas required more attention. The first area is the start-up period of a PT centre. Two of the centres had recently started activities or added significant resources, such as a new gantry treatment room, and were interested in the experiences of other centres during the start-up period. This is also of interest for the situation in the Netherlands where all four centres are scheduled to start operations in the coming two years. For this purpose, the following questions were added to the questionnaire:

- During the first year of start-up:

1. Did the number of patients per week/month fluctuate and if so, how?
2. Were you able to adapt staffing to the number of patients treated? If so, how?
3. Were you able to adapt the radiation delivery capacity (for instance closing/opening treatment rooms, changing operating hours/days) to the number of patients treated? If so, how?
4. How did you ensure patient recruitment? What was the role of the insurer in patient recruitment/referral?

Second, centres have indicated that the questions about staff satisfaction cannot be answered in depth with the current formulation, but centres are interested in this information. The current formulation of this question is intended to give a general overview of the most relevant experiences regarding staff and patient satisfaction, and the question has been reformulated to reflect this objective.

From the assessment of the quantitative indicators, it was determined that the quality assurance indicators could not be measured and were better suited for process descriptions in the qualitative section. For this purpose the following questions were added:

Quality Assurance

1. Could you describe the quality assurance process used to calibrate treatment delivery with the treatment plan?
2. Could you describe your experience in optimising this process?
3. Do you use Monitor units and/or Gamma index methodology to calibrate quality assurance procedures and if so, what are your experiences and what is the tolerance required?

The final questionnaire can be found in Appendix 3.

3.3 Systemic literature review

The total number of results was 42. Query one returned no results in Pubmed and two in Scopus. Query two returned eleven results in Pubmed and 29 in Scopus. Ten results were duplicates, 22 results were excluded after reading the abstract and five after having been read in full. Five papers were included in the study. From the references of these papers another four papers were included. A schematic overview of the selection process can be found in figure 3. An overview of the included papers, their methods, data classification according to Vieira et al. (65), objectives and the indicators used can be found in Table 9.

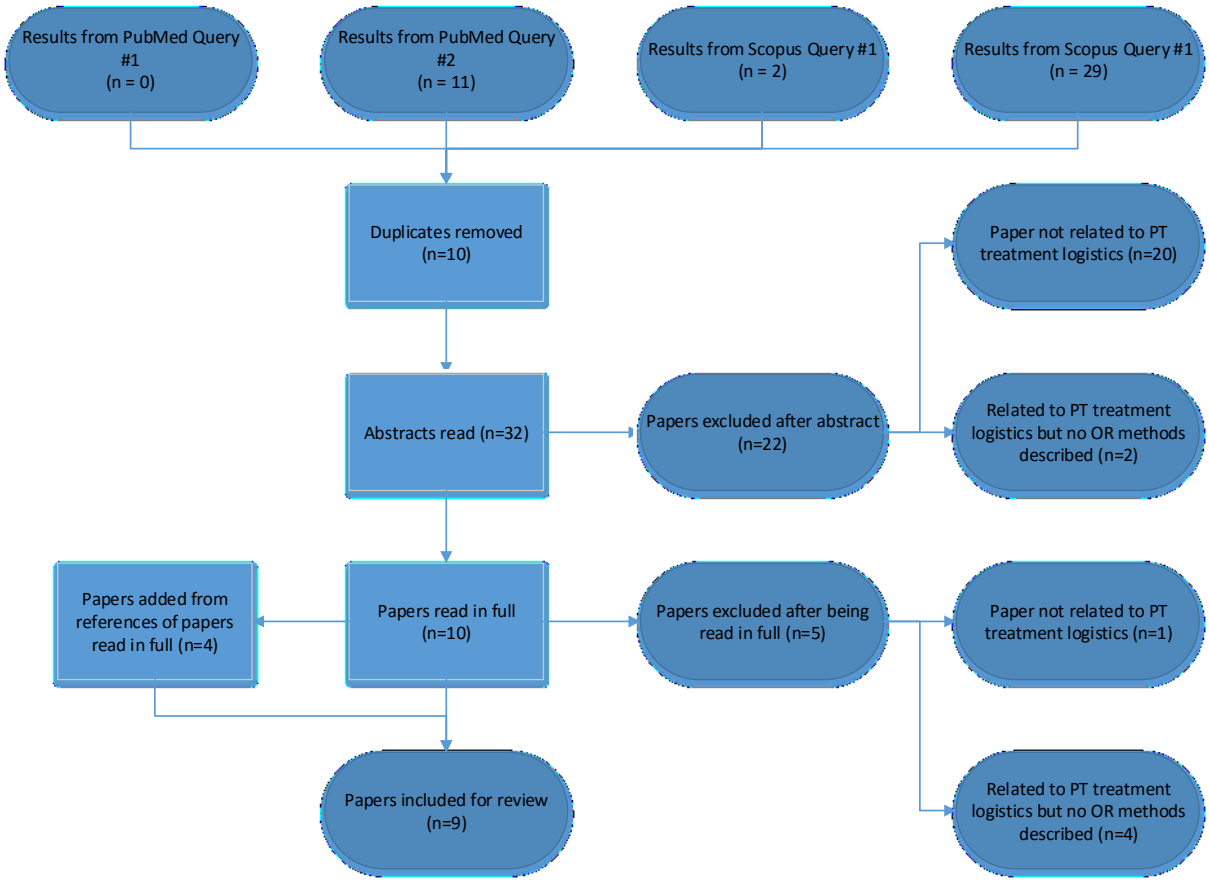

Figure 3: Overview of literature selection process

Bolsi et al. (66) have modelled the effects of positioning the patient for treatment outside of the gantry. This model has been expanded by Fava et al. (67) to apply to centres of different size. Their studies show the effects of removing the positioning process outside the bottleneck situation that occurs in the treatment rooms. Results show that under standard circumstances, remote positioning can increase the throughput in smaller centres with one or two treatment rooms. When a centre has three or more treatment rooms other factors come into play, such as the number of available imaging rooms, and without extra resources the waiting time for patients can increase to such an extent that the positioning might not be accurate at the time of treatment. Advancements in beam switching time and imaging speed can lead to better results for in-room positioning. These two papers use actual data from two

hospitals as input for the time parameters and sample these numbers to define a range of variability for the output. This means that these times can also be compared against the results of the data gathered through the proposed indicator set.

Price, Golden, Wasil & Zhang (68) and Price (69) have built a simulation model to improve the patient throughput of a PT facility. This research continues on the work done by Fava et al. (67) and uses a simulation model to investigate further possibilities for facility layout and resource optimisation. Throughput and waiting times are determined for a facility with anywhere between two to six gantry rooms. This model can be used to calculate several key performance values for stakeholders, such as the total amount of patients treated, idle times and waiting times. The research shows a decreasing economy of scale for facilities with increasing numbers of resources due to the model being based on a centre having only one beam generator (cyclotron/synchrotron), which is a standard situation. The extended research (69) adds additional scenarios such as inpatient/outpatient mix, block scheduling, patient arrival reliability, equipment failures and anaesthesia. These papers give a great amount of insight into the variability of centres parameters, and the simulation is one of the most extensive published in this field. It uses a large number of indicators that are also proposed in this study and can be used as a starting point for further research after the results of the benchmark.

Aitkenhead et al. (70) have built a Monte Carlo simulation model for a proposed UK PT centre and benchmarked their model against the MD Anderson, Houston, USA, PT centre. The model calculates the maximum throughput of a facility, patient waiting time and beam idle time under a case mix derived from the MD Anderson data but does not use a schedule or block planning as the extended Price model does. A sensitivity analysis was performed to study the effects of variation in the patient set-up time, beam switch time and caseload complexity. Last, a simulation of a two-cyclotron situation has been done. The authors conclude that the model is a good fit to the real-world realised throughput.

Gedik, Zhang & Rainwater (71) describe a Markov model to optimise adherence to a pre-determined patient mix. A balanced patient mix is important to predict access times, workload and revenue stream: The length of a treatment slot, beam time and gantry use is determined by the characteristics of the patient. The authors intend to maximise the number of patients treated while adhering to a profitable patient mix. The use of a Markov model allows for the selection of multiple options instead of a single mathematically optimal solution and gives more flexibility to schedulers. This paper is also commendable for its related work section, which gives an excellent overview of the literature of admissions planning optimisation in radiotherapy.

Men (72) has written a linear constraints model to optimise appointment planning. The model attempts to optimise the amount of fractions delivered by a centre within operational parameters and a pre-determined case mix based on data from the University of Florida. Patients are defined in categories with defined characteristics, and a penalty is applied when the desired number of patients treated

within a category is not met. Further constraints used are gantry specialisation, starting date restrictions, anaesthesia and multi-fraction treatment days.

A paper by Wang, Marcon & Pomier (73) also covers the subject of admission planning through constraints programming. The authors try to maximise the number of patients treated by programming an admission schedule that takes into account patient priority, required time and resources, and the amount of revenue a patient provides. The resulting model provides decision support for PT centres as to which patients can be treated in a timely manner within the constraints set by the business model of the centre and which need to be referred to other centres.

Cao et al. (74) use integer programming to reduce the number of energy levels required for a fraction delivery through Intensity Modulated Proton Therapy (IMPT). Although this paper concerns dose planning and would therefore fall outside the scope of the benchmark, one of the starting points of this research was to reduce the amount of time required for the fraction delivery, and the resulting model has direct implications for the optimisation of patient throughput. The solution proposed by the authors has lead to a reduction of energy levels required ranging from 11% to 26.5%, depending on the tumour type. This translates to a gantry time reduction of 12 to 126 seconds on the cases tested in this paper.

The results of the literature study show that most of the indicators proposed for the benchmark are also used in the models defined in the available studies. This concurrence implies that results from the benchmark can be used in existing models to improve facilities with minimal adaptation. The simulation studies show that for correct analysis of multi-field treatment plans, two indicators need to be added: beam switch time, which can be defined as time field started – time beam requested, and time per field, defined as time field finished – time field start. This allows a correct calculation of the beam time per patient when a multi-field treatment plan is executed while the beam is used for another patient during repositioning of the gantry head.

Table 9: Included papers and core information

Author(s) & Title	Method and implementation (65)	Optimization Objective	Indicators	Results
Bolsi, A., Lomax, A.J., Pedroni, E., Goitein, G., Hug, E. (2008) (66) Experiences at the Paul Scherrer Institute With a Remote Patient Positioning Procedure for High-Throughput Proton Radiation Therapy	Monte Carlo model III: Computational experiments show benefits to client	Patient Throughput	No. of treatment rooms Appointment frequency Mean positioning and preparation time Mean time per field Mean fields per plan Time to switch beam between treatment rooms Transfer time between CT and treatment gantry Gantry rotation time between fields treatment day duration	reduce positioning errors to below 2.5 mm and increase beam utility in the treatment room.
Fava et al. (2012) (67) In-gantry or remote patient positioning? Monte Carlo simulations for proton therapy centers of different sizes	Monte Carlo Simulation III: Computational experiments show benefits to client	Patient throughput inter-patient wait time	Number of gantries Working hours Number of transporters Times: -Imaging -Positioning -Move to gantry -Treatment -Beam switch -move after treatment -discharge	Single gantry average 20% more patients. Range: +45%, fast transporter / slow ICS to-14% slow transporter / and fast ICS. two gantries average 10% more patients Range +32% to-12%

S Price, B Golden, E Wasil, HH Zhang (2013) (68) Optimizing throughput of a multi-room proton therapy treatment centre via simulation Price (2015) (69) Applying operations research models to problems in health care (PhD Thesis)	Simulation II: Computational experiments with real data	Patient throughput (fractions delivered) Gantry wait time Excess gantry time Gantry utilization Inpatient/outpatient distribution Block scheduling	Number of gantries Working hours Number of fields (patient mix) Patient lateness % outpatient Block size Priority system Times: -Imaging -Move to gantry -Preparation (positioning) -First field -(Gantry realignment) -(other fields) -Discharge from gantry	Reduction of avg. Total wait time by 2 minutes. Gantry wait time by 37s/patient. little extra wait time added (about 6%), in switching from individually scheduled arrivals to block scheduling in the presence of early and late patient arrivals
Aitkenhead et al. (2012) (70) Modelling the throughput capacity of a single-accelerator multitreatment room proton therapy centre	Monte Carlo Simulation III Computational experiments show benefits to client	Patient throughput Beam waiting time Utilization %	Patient mix Number of gantries Equipment uptime Times: -patient set-up -anaesthesia set-up -equipment set-up -beam switch -beam delivery	good agreement between the modelled (140¡4 fractions per day) and reported (133¡35 fractions per day) throughputs
Gedik, Zhang, Rainwater (2016) (71) Strategic level proton therapy patient admission planning: a Markov decision process modeling approach	Markov Model II: Computational experiments with real data	Gantry utilization Patient mix adherence	Number of gantries Patient mix Times: -Scheduling block	Nearly identical solutions for aggregate and regular Markov model. Aggregate uses less computing time.

Men (2009) (72) Optimization models for radiation therapy : treatment planning and patient scheduling (PhD Thesis)	Linear programming (constraints programming) III: Computational experiments show benefits to client	Patient throughput Appointment time Patient mix adherence Patient satisfaction	Number of gantries Working hours New patient starting hours First-time patients Anaesthesia required Anaesthesia team availability Gantry specialization Times: -Intra-fraction -Snout changing -Treatment -appointment time deviation	#fractions per day under different scenarios: 77 to 126 (base 100). Increased number of paediatric patients.
Wang, Marcon, Pomier (2011)(73) Online scheduling for a hadrontherapy center	Linear programming (constraints programming) II: Computational experiments with real data	Patient throughput (Revenue) Overtime	Opening hours Patient mix Patient priority Times: -Treatment	Decision support feasible for both off- and online scheduling
Cao W, Lim G, Liao L, Li Y, Jiang S, Li X, Li H, Suzuki K, Zhu XR, Gomez D, Zhang X. (2014) (74) Proton energy optimization and reduction for intensity-modulated proton therapy.	iterative mixed-integer programming optimisation IV: Results of computational experiments validated by client	Treatment time proton beam energy state	Number of fields Number of energy states Total delivery time Number of spots	Reduction of energy levels required from 11% to 26.5%, gantry time reduction of 12 to 126 seconds.

4. Discussion

To our knowledge, this study is the first attempt to determine PT benchmark attributes that are validated by prospective participants. The benchmark methodology used required that the decision what to benchmark was made at the start of the study. This meant that a focus on the logistical processes was immediately adapted. However, from the feedback on the developed indicators and questionnaire, it is noticed that the patient, who is not identified as a definitive stakeholder for the scope of the benchmark, is a definitive stakeholder in the eyes of the centres. This stakeholder is not well represented in the developed indicators. Although this is acceptable as patients have little influence on the processes studied the outcomes of this process to the patients are very relevant to the responding centres. As the importance of outcomes in the definition of value in healthcare is growing it is advisable to take the outcomes into account in any situation where a process is analysed. The recommended approach to this situation is to carefully research the desired outcomes of prospective benchmarking partners before the stakeholder analysis. Any stakeholder that is not included in the definitive category through their influence on the process but is referred as important for outcomes by the centre should be included in the definitive category. This is especially true for stakeholders that possess two out of three attributes. Doing so would create several scenarios for the benchmark, depending on the stakeholders present. For instance, a more patient centred approach would take into account indicators such as adherence to preferred time slots or waiting times for companions while a more insurer-based approach would focus on maximum cost reduction with less attention to patient and staff indicators.

4.1 Quantitative indicator selection

The most important limitation in the determination of the indicator set is the relatively low number of centres that have given feedback on the quantitative section: four. Of these four, one centre has given in-depth information on the amount of information available, possible data points and bottlenecks. Two centres have given thorough feedback on the availability of data and the limitations of their output but have not given feedback on possible data points. The last centre has only given an assessment on the availability of data. This means that although this set of indicators is feasible for these centres, the generalisability of this set to other centres is unknown. However, the literature study shows that the indicators proposed for this study have also been extracted from to other PT centres and used in simulation studies. It is therefore expected that the proposed indicator set is feasible for application in existing models and can be applied to other centres for future benchmarking.

The current focus on the delivery part of the study excludes one of the main indicators for the patients: access time. This indicator is unequivocally entangled with the realised appointment schedule: the choices and limitations of the schedule and accepted patient mix determine the access time. Because patients are given a treatment starting date as soon as they are accepted, the true access time is outside

of the scope of this benchmark. To determine performance in terms of the patient as a stakeholder it may be of value to include the access time and case mix in the benchmark but this would significantly widen the scope of the benchmark: Although the treatment plan is supposed to be complete any time before start of treatment this is not possible without the resources available in the planning and physics department. For an effective benchmark of the access time, it is therefore not only required to know the patient mix and associated scheduling characteristics, which is included in the indicators, but also the workings of the diagnosis and treatment planning procedure. This would require new process analysis and indicator development for the pre-treatment phase.

From the assessment of indicators, feasibility of data extraction was identified as the primary restriction on the acceptance of the quantitative part of the benchmark. While most information was available through one of several software systems, the required effort to extract the data could be more than acceptable under current circumstances as there is no straightforward (or automated) method to generate a data dump to be used for quantitative analysis. Sampling data could limit the amount of effort required, but a site visit to one of the centres made clear that seasonal influences are present and it is difficult to determine a period that samples the right patient mix in sufficient numbers for statistical analysis. For the current situation, it is advisable to work with the manufacturer of the patient management software to find a workaround for this problem. The popularity of benchmarking is increasing, and the expected future situation in the Netherlands is ideally suited to benchmark the four planned centres. Action should be taken to ensure that the means to generate comparable data is part of the development of the centres software systems, for instance by making the possibility to generate data dumps part of the purchasing tender for the patient management software.

4.2 Systematic literature review

Considering the results of the systematic literature review, it is remarkable that the amount of papers from the primary search was low: only five papers were included. The secondary search within the references and citations of papers found through the systemic queries produced another four papers. This could imply that the search queries and databases used were not well suited or still too narrow to produce the expected results. However, an extension of the search to the Web of Science and Picarta databases produced no results that were not found through PubMed and Scopus. This indicates that the choice of database is not the cause of the limited amount of papers found. A Google scholar search did produce some papers found through the references and citations but also returned thousands of results that were not relevant: Google scholar is not suitable for executing a systematic search strategy. The apparent reason for the lack of results is that the subject of operations research is not clearly defined in the medical research databases; this is also observed through the fact that the second search query returned far more results than the first. Also, OR uses several terms, such as planning, that are used in another context in particle therapy. It is therefore recommended that an OR literature search in medical

papers is done through well-defined contextual search terms that return the papers on the OR subject one is interested in.

Most published models use Monte Carlo simulation methods. This is no coincidence: Monte Carlo models are best suited to provide information on scenarios with several parameters that can vary in magnitude. However, the variance in these simulations is modelled by a probability distribution and the models are not in agreement as to which distributions to use. This means that while models may be a good fit to an existing situation, this must be revisited for the specific expected distribution of each simulated centre. The data gained in the benchmark can be used to better estimate the best distribution for simulation studies that can be applied to multiple centres.

Linear programming can be used to optimise one single parameter. These studies are effective for specific scenarios but other parameters can only be controlled by constraining. This implies that the parameter to optimise must be carefully chosen to align with the stakeholder analysis, and an in-depth knowledge of the preferences and limits of all stakeholders should be known in order to set the right constraints.

It is notable that significant effort is taken to optimise patient throughput, patient mix and waiting time. These indicators belong to management and patient stakeholders, but very little attention is paid to staff indicators. All models assume that unlimited staff is available in all departments and that every preparation step is complete before the start of the model. This is logical considering the objectives of the simulations but not realistic given the costs of staff and other resources.

Optimisation of non-gantry resources is especially important in the planned PT centres in The Netherlands. As these are all relatively small, 2 or 3 treatment rooms each, it is unlikely that high beam utilisation can be achieved due to the processes other than irradiation that takes place in the treatment rooms. Optimisation of these processes can lead to a greater increase in utilisation than in centres with higher numbers of treatment rooms. Additionally, remote positioning such as described by Bolsi et al. and Fava et al. is more suitable to smaller centres. However, future developments in imaging, such as MRI-assisted PT, lead to high-quality imaging equipment being available inside the treatment rooms and the obsolescence of remote positioning.

4.3 Future research

The next logical step in this project would be to perform the benchmark and measure the indicators. Responding centres have indicated that the required information is available and valid for their centres. However, this does not mean that the information supplied by the centres can be directly compared. For instance, the data entry points for the particle accelerator system are dependent on the machine used by a centre. The same principle applies to appointment time, anaesthesia time, etc: data supplied will be what is registered by a centre but starting time registration; end points, etc. are not necessarily

uniform between centres. Therefore, the main issue to be kept in mind when performing the benchmark is to correct for differences in data entry.

The presented list of indicators has been assessed by centres in four different countries, each with their culture of healthcare delivery and reimbursement. It is thus expected that the benchmark can be expanded to include other centres without much adaptation, but each centre needs to make an assessment. To make data as comparable as possible, it is advised to include at least one user of every major producer of PT equipment and patient management software to increase knowledge of data entry points and comparability.

The responding centres have indicated that the use of both hypofractionation and adaptive planning can influence the validity of the current benchmark parameters. Hypofractionation is a radiation treatment technique that delivers more than the regular amount of radiation to a patient, using a smaller amount of longer than regular fractions. This decreases the number of fractions that can be delivered in a treatment day but may lead to less variation in the schedule. Adaptive planning divides the treatment into several stages, for instance, five five-day stages for a 25-fraction treatment, and creates a new treatment plan for every stage. Creating multiple treatment plans instead of one requires additional imaging and verification resources; this extra load has to be taken into account.

The results of the OR literature search show a clear knowledge gap concerning the use of shared resources such as nursing and anaesthesia staff. Only one centre was a true stand-alone outpatient clinic, the other responding clinics are part of a larger hospital and depend in some way on the resources supplied by this hospital. All reviewed studies simulate a centre with no outside influence and unlimited staffing. The way staff interacts with the patient and the technological process is well suited for a simulation study that includes facility layout optimisation.

Current models use either an average with standard deviation and range limits to determine a possible range of variation or a block planning with averages in the indicators used for simulation. While these simulations indicate that a high utilisation is not acceptable because of bottlenecks and the requirement for some slack in the process, no study to date has determined how this slack should be quantified in a PT setting. Simulation models can be developed that allow slack to be included in the calculation of an appointment schedule. The data generated by the benchmark would be ideally suited for determination of a statistical distribution and the resulting slack calculations. It is expected that this will improve the scheduling efficiency and throughput.

Centres have indicated that staff satisfaction is not very well known and are interested in the experiences of other centres. While patient satisfaction is constantly monitored by the centres, no such system exists for staff satisfaction. This can best be resolved by developing an anonymous questionnaire to be provided to staff members, ideally at regular intervals.

The models developed by Gedik, Zhang & Rainwater and Wang, Marcon & Pomier use the amount of revenue that patients create in a comparison against the required resources and patient mix adherence. These kind of models are very heavy on computational resources but can be simplified. If these models are reversed, they can be used to calculate a price point for a specific patient and access time. In a true market setting, this can be used to create a digital market in which insurers can ask for a price quote for their patients: this would lead to higher amounts of competition in the healthcare market and a lower price for consumers. The applicability of these methods in the strictly regulated PT market is limited: Due to the high costs of capital, limited patient mix in comparison to radiotherapy and limited numbers of centres is it easy to distort this market by (temporarily) setting an unreasonably low price to gain market advantage. Additionally, detailed knowledge about the price structure of medical services would be required to operate such a system; this information is likely unknown to hospital staff. This lack of knowledge is subject to intense discussion about the structure of the healthcare market and using computer aided pricing models would require hospitals to restructure their business models.

Last, the situation in the Netherlands, with four planned PT centres and the related societal expenses, are a unique field of market forces in healthcare. Because of the discussion concerning the amount of PT centres to be built and/or contracted by healthcare insurers, the development of PT in The Netherlands would be an ideal experiment to be analysed with methods such as Porters (75) five/six forces model. This would not only give valuable insight into the market forces that govern PT but also in the challenges of implementing highly expensive medical innovations.

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Appendix A: Qualitative questionnaire before assessment

General questions

1. What are the centres regular operating hours? Please specify when it differs per week and/of weekend day.
2. How many days per year is the centre in operation? (based on tactical planning and not realised schedule)
3. How much inpatients(patients who are in 24-hour care of the facility or a associated hospital) does the centre (intend to) treat and for what tumour types?
4. What is the influence of insurance companies on the treatment approval? Do you have an agreement on service levels with the insurance companies? How much time is usually required for the insurer to give approval? What is the maximum waiting time until treatment is started without approval? How many patient are treated per year without 1) insurance and 2) approval of the insurance company? Is this number rising, steady or lowering in the past three years?
5. What are the guaranteed service level agreements being used with the suppliers?
6. What are the quality service levels that you which to achieve? Which quality accreditation, if any, are you adhering to or aiming for?
7. What are the necessary choices being given to the patients to decide on the treatment planning? (shared decision making)
8. How many service time outs are being included in the year planning and how long do these take? What is the difference between the year planning and realised service timeout (2013, 2014, 2015)?
9. What is your patient's general opinion about operational quality and efficiency? What are the main problems you have encountered regarding patient satisfaction and how have you solved those?
10. What is your staff's general opinion about operational quality and efficiency? What are the main problems you have encountered regarding staff satisfaction and how have you solved those?
11. What percentage of staff time is, to your best knowledge, direct time (spent on patients)? Please specify per staff type.

Appointment scheduling

To obtain information as to how resource scheduling and appointment planning processes are shaped in participating centres, participants are asked to provide detailed descriptions of the following processes:

1. The independent verification of patient's treatment plans.

2. Tactical (block) planning process and methods, which result in a (multi-) month general division of accelerator time (if applicable).
3. The operational planning process and methods, meaning the actual patient appointment scheduling.

When these processes differ between categories stated in table 1, please specify.

Treatment execution

To gain information as to how the appointment planning and treatment are executed, participants are asked to construct a flowchart which contains, per individual process step, the following information:

1. Name of process step (for instance immobilization)
2. Resources and materials required (i.e. mask, gantry) → technological process
3. Staff required → professional process
4. Patient required? → patient process
5. Information required → administrative process
6. Physical space (room) required
7. Processes required to be complete before start.
8. General indication of time required to complete step (expert opinion)

Appendix B: Quantitative indicators before assessment

1.Staff workload	
numerator	*denominator*
# staff (preferably per staff type: oncologist, physicist, nurse, technician etc.) in FTE.	Number of fractions per year (number of patients per tumour type * average number of fractions per type), stratified per tumour type and adult/children.
2.Cancer type distribution	
numerator	*denominator*
Number of fractions per tumour type per year	Total amount of fractions per year.
3.Average fractions per patient per tumour type	
numerator	*denominator*
Number of fractions per tumour type per year	Number of patients per tumour type per year
4.Type and number of proton beam treatment rooms	
numerator	*denominator*
Number of (IMPT) gantries, number of horizontal beam etc.	Number of fractions per year (number of patients per tumour type * average number of fractions per type), preferably stratified per tumour type and adult/children.
5.Tumour type capacity per treatment room	
numerator	*denominator*
number of tumour types treated in centre that can be treated in a particular room (gantry, horizontal beam etc.)	Total number of tumour types treated in centre.
6.Facility use outside of treatment stations	
numerator	*denominator*
number of anaesthetic rooms	Total number of fractions requiring anaesthesia per year.
7.Time required for treatment plan verification	
numerator	*denominator*
Number of days (hours) required for treatment verification per patient, per tumour type	Number of patients per tumour type
8.Revision after treatment verification	

numerator	*denominator*
Number of plans requiring revision after verification, per tumour type per year	Total number of plans submitted, per tumour type per year.
9.Time required for revision	
numerator	*denominator*
Total number of days (hours) between failing independent verification and next independent verification.	total number of plans submitted for revision, per tumour type per year.
10.Treatment access time	
numerator	*denominator*
Total number of days between treatment verification complete and first fraction appointment, per patient, per tumour type	Number of patients per year per tumour type
11.Time between fractions	
numerator	*denominator*
Total number of days between fractions per year, per tumour type	Number of fractions -1 (first fraction is separate measure) * number of patients per year, per tumour type
12.Treatment completion time	
numerator	*denominator*
Total number of days between first and last fraction, per tumour type and number of fractions	Total number of patients per year, per tumour type and number of fractions
13.Patient on-site waiting time	
numerator	*denominator*
Total minutes of patient waiting time between last communicated scheduled appointment time and start of appointment, per tumour type per year	Total number of fractions per year per tumour type
14.No-shows	
numerator	*denominator*
Total number of fractions not delivered due to patient not available, per tumour type	Number of fractions per year, per tumour type
15.Patient lateness	

numerator	*denominator*
Number of minutes of patient being late for appointment per appointment, per tumour type	Number of fractions per year per tumour type
16.Staff overtime	
numerator	*denominator*
Number of minutes worked after official working hours, per staff type per year.	Number of working days per year.
17.appointment duration	
numerator	*denominator*
Number of minutes planned in treatment room, per patient, per tumour type.	Number of fractions planned per patient, per tumour type.
18.Radiation time as part of appointment time	
numerator	*denominator*
Number of minutes of beam in chamber per patient, per tumour type	Number of minutes treatment room allocated, per patient, per tumour type
19.Proton beam not on patient	
numerator	*denominator*
Number of minutes beam not on patient per year (=number of minutes beam available– numerator of #18)	Number of minutes beam available for treatment per year
20.Proton beam unavailability	
numerator	*denominator*
Number of minutes of waiting time due to beam unavailable while patient ready, per tumour type per year	Number of minutes of radiation time (including waiting time) per tumour type per year
21.Treatment room utilisation (immobilisation)	
numerator	*denominator*
Number of minutes required for immobilisation, per patient per tumour type	Number of minutes treatment room allocated, per patient, per tumour type
22.Treatment room utilisation (positioning)	
numerator	*denominator*
Number of minutes required for positioning, per patient,	Number of minutes treatment room allocated, per patient, per

per tumour type	tumour type
23.Positioning accuracy	
numerator	*denominator*
Number of millimetres of movement, per tumour type per year	Number of fractions, per tumour type per year.
24.Treatment room utilisation (nozzle adjustment)	
numerator	*denominator*
Number of minutes required for nozzle adjustment, per tumour type per year	Number of minutes realised in appointment schedule, per tumour type per year
25.Time required for anaesthesia	
numerator	*denominator*
Number of minutes required for anaesthesia, per patient, per tumour type.	Number of fractions, per patient, per tumour type.
26.Unscheduled maintenance	
numerator	*denominator*
Number of minutes of unscheduled maintenance during working hours, per year.	Number of minutes within working hours, per year
27.Other downtime	
numerator	*denominator*
Number of minutes lost to other causes, per year	Number of minutes within working hours, per year
28.Quality assurance time	
numerator	*denominator*
Number of minutes of planned quality assurance during working hours, per year.	Number of minutes within working hours, per year

Appendix C: Qualitative questionnaire after assessment

General questions

1. What are the centres regular operating hours? Please specify when it differs per week and/of weekend day.
2. How many days per year is the centre in operation? (based on tactical planning and not realised schedule)
3. How much inpatients(patients who are in 24-hour care of the facility or a associated hospital) does the centre (intend to) treat and for what tumour types?
4. What is the influence of insurance companies on the treatment approval? Do you have an agreement on service levels with the insurance companies? How much time is usually required for the insurer to give approval? What is the maximum waiting time until treatment is started without approval? How many patient are treated per year without 1) insurance and 2) approval of the insurance company? Is this number rising, steady or lowering in the past three years?
5. What are the guaranteed service level agreements being used with the suppliers?
6. What are the quality service levels that you which to achieve? Which quality accreditation, if any, are you adhering to or aiming for?
7. What are the necessary choices being given to the patients to decide on the treatment planning? (shared decision making)
8. How many service time outs are being included in the year planning and how long do these take? What is the difference between the year planning and realised service timeout (2013, 2014, 2015)?
9. What is your patient's general opinion about operational quality and efficiency? What are the main problems you have encountered regarding patient satisfaction and how have you solved those?
10. Have you had determined yourself or had any comments from your staff regarding problems in scheduling and/or staffing? For instance high fluctuation in work intensity, understaffing, overstaffing etc? If so, how have you reacted to these situations?
11. What percentage of staff time is, to your best knowledge, direct time (spent on patients)? Please specify per staff type.

Appointment scheduling

To obtain information as to how resource scheduling and appointment planning processes are shaped in participating centres, participants are asked to provide detailed descriptions of the following processes:

1. The independent verification of patient's treatment plans.

2. Tactical (block) planning process and methods, which result in a (multi-) month general division of accelerator time (if applicable).
3. The operational planning process and methods, meaning the actual patient appointment scheduling.

Start-up phase

During the first year of start-up:

1. did the number of patients per week/month fluctuate and if so, how?
2. Were you able to adapt staffing to the number of patients treated? If so, how?
3. Were you able to adapt the radiation delivery capacity (for instance closing/opening treatment rooms, changing operating hours/days)to the number of patients treated? If so, how?
4. How did you ensure patient recruitment? What was the role of the insurer in patient recruitment/referral?

Quality Assurance

Could you describe the quality assurance process used to calibrate treatment delivery with the treatment plan? Could you describe your experience in optimizing this process ? Do you use Monitor units and/or Gamma index methodology to calibrate quality assurance procedures and if so, what are your experiences and what is the tolerance required?

Treatment execution

To gain information as to how the appointment planning and treatment are executed, participants are asked to construct a flowchart of the processes described in figure 1. We would like you to provide, per individual process step, the following information:

1. Name of process step (for instance immobilization)
2. Resources and materials required (i.e. mask, gantry) → technological process
3. Staff required → professional process
4. Patient required? → patient process
5. Information required → administrative process
6. Physical space (room) required
7. Processes required to be complete before start.
8. General indication of time required to complete step (expert opinion)

Appendix D: Results of systematic literature search

Pubmed Query 1

No results

Pubmed Query 2

Title	Author	Details	Read	inclusion	reason
Carbon-Ion Pencil Beam Scanning Treatment With Gated Markerless Tumor Tracking: An Analysis of Positional Accuracy.	Mori S, Karube M, Shirai T, Tajiri M, Takekoshi T, Miki K, Shiraishi Y, Tanimoto K, Shibayama K, Yasuda S, Yamamoto N, Yamada S, Tsuji H, Noda K, Kamada T.	Int J Radiat Oncol Biol Phys. 2016 Jan 20. doi:pii: S0360-3016(16)00024-9. 10.1016/j.ijrobp.2016.01.014. [Epub ahead of print]	abstract	excluded	not related to treatment logistics
Strategic level proton therapy patient admission planning: a Markov decision process modeling approach.	Gedik R, Zhang S, Rainwater C.	Health Care Manag Sci. 2016 Jan 25. [Epub ahead of print]	full	included	
Spatial mapping of the biologic effectiveness of scanned particle beams: towards biologically optimized particle therapy.	Guan F, Bronk L, Titt U, Lin SH, Mirkovic D, Kerr MD, Zhu XR, Dinh J, Sobieski M, Stephan C, Peeler CR, Taleei R, Mohan R, Grosshans DR.	Sci Rep. 2015 May 18	abstract	excluded	not related to treatment logistics
Proton energy optimization and reduction for intensity-modulated proton therapy.	Cao W, Lim G, Liao L, Li Y, Jiang S, Li X, Li H, Suzuki K, Zhu XR, Gomez D, Zhang X.	Phys Med Biol. 2014 Nov 7	full	included	
Predicting the sensitivity to ion therapy based on the response to photon irradiation--experimental evidence and mathematical modelling.	Mohanty C, Zielinska-Chomej K, Edgren M, Hirayama R, Murakami T, Lind B, Toma-Dasu I.	Anticancer Res. 2014 Jun	abstract	excluded	not related to treatment logistics

In search of the economic sustainability of Hadron therapy: the real cost of setting up and operating a Hadron facility.	Vanderstraeten B, Verstraete J, De Croock R, De Neve W, Lievens Y.	Int J Radiat Oncol Biol Phys. 2014 May 1	full	excluded	not specific enough to PT logistics or OR methods
Ion radiography as a tool for patient set-up and image guided particle therapy: a Monte Carlo study.	Depauw N, Dias MF, Rosenfeld A, Seco JC.	Technol Cancer Res Treat. 2014 Feb	abstract	excluded	not related to treatment logistics
Simulating demand for innovative radiotherapies: an illustrative model based on carbon ion and proton radiotherapy.	Pommier P, Lievens Y, Feschet F, Borras JM, Baron MH, Shtiliyanova A, Pijls-Johannesma M.	Radiother Oncol. 2010 Aug	full	included	
Proton beam radiotherapy versus three-dimensional conformal stereotactic body radiotherapy in primary peripheral early-stage non-small-cell lung carcinoma: a comparative dosimetric analysis.	Macdonald OK, Kruse JJ, Miller JM, Garces YI, Brown PD, Miller RC, Foote RL.	Int J Radiat Oncol Biol Phys. 2009 Nov 1	abstract	excluded	not related to treatment logistics
The National Center for Oncological Hadron Therapy: status of the project and future clinical use of the facility.	Orecchia R, Fossati P, Rossi S.	Tumori. 2009 Mar-Apr	full	excluded	No OR methods described
Comparison between in-beam and offline positron emission tomography imaging of proton and carbon ion therapeutic irradiation at synchrotron- and cyclotron-based facilities.	Parodi K, Bortfeld T, Haberer T.	Int J Radiat Oncol Biol Phys. 2008 Jul 1	abstract	excluded	not related to treatment logistics

Scopus Query 1

Title	Author	Details	Read	inclusion	reason
Scheduling guidelines for a multi-room proton therapy treatment center	Price, S., Golden, B., Wasil, E., Zhang, H.H	Modelling and Simulation 2014 - European Simulation and Modelling Conference, ESM 2014 pp. 283-287	full	included	
Status and prospect of the activity at the Moscow meson factory (MMF)	Akulinichev, S.V., Vyalov, G.N., Grachev, M.I.	Atomnaya Energiya 94 (1), pp. 76-81	abstract	excluded	does not concern PT

Scopus Query 2

Authors	Title	Year	Source title	Volume	Issue	Art. No.	Page start	Page end	Read	inclusion	reason
Gedik, R., Zhang, S., Rainwater, C.	Strategic level proton therapy patient admission planning: a Markov decision process modeling approach	2016	Health Care Management Science				1	17	duplicate		
Stokkevåg, C.H., Engeseth, G.M., Hysing, L.B., Ytre-Hauge, K.S., Ekanger, C., Muren, L.P.	Risk of radiation-induced secondary rectal and bladder cancer following radiotherapy of prostate cancer	2015	Acta Oncologica	54	9		1317	1325	abstract	excluded	not related to treatment logistics
Guan, F., Bronk, L., Titt, U., Lin, S.H., Mirkovic, D., Kerr, M.D., Zhu, X.R., Dinh, J., Sobieski, M., Stephan, C., Peeler, C.R., Taleei, R., Mohan, R., Grosshans, D.R.	Spatial mapping of the biologic effectiveness of scanned particle beams: Towards biologically optimized particle therapy	2015	Scientific Reports	5		9850			duplicate		
Cao, W., Lim, G., Liao, L., Li, Y., Jiang, S., Li, X., Li, H., Suzuki, K., Zhu, X.R., Gomez, D., Zhang, X.	Proton energy optimization and reduction for intensity-modulated proton therapy	2014	Physics in Medicine and Biology	59	21	6341	6341	6354	duplicate		

Vanderstraeten, B., Verstraete, J., De Croock, R., De Neve, W., Lievens, Y.	In search of the economic sustainability of hadron therapy: The real cost of setting up and operating a hadron facility	2014	International Journal of Radiation Oncology Biology Physics	89	1		152	160	duplicate		
Depauw, N., Dias, M.F., Rosenfeld, A., Seco, J.C.	Ion radiography as a tool for patient set-up & image guided particle therapy: A monte carlo study	2014	Technology in Cancer Research and Treatment	13	1		69	76	duplicate		
Mansur, D.B.	Incorporating a compact proton therapy unit into an existing National Cancer Institute-designated comprehensive cancer center	2014	Expert Review of Anticancer Therapy	14	9		1001	1005	abstract	excluded	No OR methods described
Sheng, K., Dong, P., Gautam, A., Cheng, C.W., Ruan, D., Low, D., Cao, M., Lee, S., Kupelian, P.	Evolution of ipsilateral head and neck radiotherapy	2014	Current Cancer Therapy Reviews	10	4		343	352	abstract	excluded	not related to treatment logistics
Orth, M., Lauber, K., Niyazi, M., Friedl, A.A., Li, M., Maihöfer, C., Schüttrumpf, L., Ernst, A., Niemöller, O.M., Belka, C.	Current concepts in clinical radiation oncology	2014	Radiation and Environmental Biophysics	53	1		1	29	abstract	excluded	not related to treatment logistics
Takamatsu, S., Yamamoto, K., Kawamura, M., Sato, Y., Asahi, S., Kondou, T., Tameshige, Y., Maeda, Y., Sasaki, M., Kumano, T., Gabata, T.	Utility of an initial adaptive bladder volume control with ultrasonography for proton-beam irradiation for prostate cancer	2014	Japanese Journal of Radiology	32	10		618	622	abstract	excluded	not related to treatment logistics
Iyengar, P., Westover, K., Timmerman, R.D.	Stereotactic ablative radiotherapy (SABR) for non-small cell lung cancer	2013	Seminars in Respiratory and Critical Care Medicine	34	6		845	854	abstract	excluded	not related to treatment logistics
Price, S., Golden, B., Wasil, E., Zhang, H.H.	Optimizing throughput of a multi-room proton therapy treatment center via simulation	2013	Proceedings of the 2013 Winter Simulation Conference - Simulation: Making Decisions in a Complex World, WSC 2013			6721616	2422	2431	duplicate		

Pugh, T.J., Munsell, M.F., Choi, S., Nguyen, Q.N., Mathai, B., Zhu, X.R., Sahoo, N., Gillin, M., Johnson, J.L., Amos, R.A., Dong, L., Mahmood, U., Kuban, D.A., Frank, S.J., Hoffman, K.E., McGuire, S.E., Lee, A.K	Quality of life and toxicity from passively scattered and spot-scanning proton beam therapy for localized prostate cancer	2013	International Journal of Radiation Oncology Biology Physics	87	5		946	953	abstract	excluded	not related to treatment logistics
Thörnqvist, S., Muren, L.P., Bentzen, L., Hysing, L.B., Hoyer, M., Grau, C., Petersen, J.B.B.	Degradation of target coverage due to inter-fraction motion during intensity-modulated proton therapy of prostate and elective targets	2013	Acta Oncologica	52	3		521	527	abstract	excluded	not related to treatment logistics
Wang, T., Zhang, E., Marcon, T., Pomier, P.	Decision support tool for patient recruitment in a hadrontherapy center	2011	IFAC Proceedings Volumes (IFAC-PapersOnline)	18	PART 1		10416	10421	duplicate		full artcile not available
Cotter, S.E., Herrup, D.A., Friedmann, A., MacDonald, S.M., Pieretti, R.V., Robinson, G., Adams, J., Tarbell, N.J., Yock, T.I.	Proton radiotherapy for pediatric bladder/prostate rhabdomyosarcoma: Clinical outcomes and dosimetry compared to intensity-modulated radiation therapy	2011	International Journal of Radiation Oncology Biology Physics	81	5		1367	1373	abstract	excluded	not related to treatment logistics
Tao, W., Eric, M., Pascal, P.	Online scheduling for a hadrontherapy treatment center	2011	Proceedings of the 30th Chinese Control Conference, CCC 2011			6001450	2201	2205	full	included	
Rengan, R., Maity, A.M., Stevenson, J.P., Hahn, S.M.	New strategies in non-small cell lung cancer: Improving outcomes in chemoradiotherapy for locally advanced disease	2011	Clinical Cancer Research	17	13		4192	4199	abstract	excluded	No OR methods described
Oshiro, Y., Okumura, T., Ishida, M., Sugahara, S., Mizumoto, M., Hashimoto, T., Yasuoka, K., Tsuboi, K., Sakae, T., Sakurai, H.	Displacement of hepatic tumor at time to exposure in end-expiratory- triggered-pulse proton therapy	2011	Radiotherapy and Oncology	99	2		124	130	abstract	excluded	not related to logistics

Wambersie, A., Jones, D.T.L., Gueulette, J., Gahbauer, R., Deluca Jr., P.M.	What can we learn from the neutron clinical experience for improving ion-beam techniques and high-LET patient selection?	2010	Radiation Measurements	45	10		1374	1380	abstract	excluded	not related to logistics
Pommier, P., Lievens, Y., Feschet, F., Borras, J.M., Baron, M.H., Shtiliyanova, A., Pijls-Johannesma, M.	Simulating demand for innovative radiotherapies: An illustrative model based on carbon ion and proton radiotherapy	2010	Radiotherapy and Oncology	96	2		243	249	duplicate		
Macdonald, O.K., Kruse, J.J., Miller, J.M., Garces, Y.I., Brown, P.D., Miller, R.C., Foote, R.L.	Proton Beam Radiotherapy Versus Three-Dimensional Conformal Stereotactic Body Radiotherapy in Primary Peripheral, Early-Stage Non-Small-Cell Lung Carcinoma: A Comparative Dosimetric Analysis	2009	International Journal of Radiation Oncology Biology Physics	75	3		950	958	abstract	excluded	not related to logistics
Orecchia, R., Fossati, P., Rossi, S.	The national center for oncological hadron therapy: status of the project and future clinical use of the facility	2009	Tumori	95	2		169	176	duplicate		
Bolsi, A., Lomax, A.J., Pedroni, E., Goitein, G., Hug, E.	Experiences at the Paul Scherrer Institute With a Remote Patient Positioning Procedure for High-Throughput Proton Radiation Therapy	2008	International Journal of Radiation Oncology Biology Physics	71	5		1581	1590	full	included	
Parodi, K., Bortfeld, T., Haberer, T.	Comparison Between In-Beam and Offline Positron Emission Tomography Imaging of Proton and Carbon Ion Therapeutic Irradiation at Synchrotron- and Cyclotron-Based Facilities	2008	International Journal of Radiation Oncology Biology Physics	71	3		945	956	duplicate		
Schulte, R.W.	Proton treatment room concepts for precision and efficiency	2007	Technology in Cancer Research and Treatment	6	4 SUPPL.		55	60	full	excluded	No OR methods described

Schulz-Ertner, D., Tsujii, H.	Particle radiation therapy using proton and heavier ion beams	2007	Journal of Clinical Oncology	25	8		953	964	abstract	excluded	not related to logistics
Weyrather, W.K., Kraft, G.	RBE of carbon ions: Experimental data and the strategy of RBE calculation for treatment planning	2004	Radiotherapy and Oncology	73	SUPPL. 2		S161	S169	abstract	excluded	not related to logistics
Coleman, C.N.	International Conference on Translational Research ICTR 2003 Conference Summary: Marshalling resources in a complex time	2004	International Journal of Radiation Oncology Biology Physics	58	2		307	319	full	excluded	No OR methods described

Nawoord

"In the Netherlands we say: that is another cook"

Louis van Gaal over afstuderen

Deze scriptie is zowel het begin als het eind van een lange periode. Het voltooien van het eerste is niet gelukt zonder de hulp van vele mensen. In het bijzonder wil ik de volgende personen bedanken:

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Nu gaat het volgende boek open, zonder titel maar met hoofdrolspelers. Ik houd jullie op de hoogte van de mooie dingen die het gaat brengen.

Tim.

Roosendaal, 19-07-2016