

# CANCER PLAN

## ACTION 30

(FINANCED BY THE FEDERAL PUBLIC SERVICE OF HEALTH, FOOD CHAIN SAFETY AND ENVIRONMENT)



### *Feasibility study of a Hadron Therapy Centre in Belgium*

EXECUTED BY

THE BELGIAN HADRON THERAPY CENTRE (BHTC) FOUNDATION

IN COLLABORATION WITH

BELGIAN UNIVERSITIES, UNIVERSITY HOSPITALS,  
RESEARCH INSTITUTES, EXPERTS FROM THE BELGIAN  
SOCIETY OF PAEDIATRIC HEMATOLOGY AND ONCOLOGY

AND

INTERNATIONAL EXPERTS IN HADRON THERAPY

**GUIDED BY THE CANCER PLAN UNIT**

REVIEWED BY THE STEERING COMMITTEE OF ACTION 30

EXTENDED EXECUTIVE SUMMARY - MAY 10<sup>TH</sup>, 2013

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**(Financed by the Federal Public Service of Health, Food Chain Safety and Environment)**

**Guided by the Unit Cancer Plan**

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## ■ *Feasibility Study of a Belgian Hadron Therapy Centre*

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In March 2010 the 7 Belgian University Hospitals, SCK-CEN and the University of Namur announced their will to participate in a common feasibility study for a hadron centre in Belgium within the framework of the Cancer Plan Action 30, Federal Office of Health and Social Affairs.

On 20/4/2011 the Federal Office granted the Belgian Hadron Therapy Centre Foundation to coordinate a first phase feasibility study to assess the number of eligible patients in Belgium and to check the feasibility of such centre in terms of investment costs, of operating costs and of the resulting treatment costs.

The 7 University Hospitals, all members of the Belgian Hadron Therapy Centre Foundation have been requested to cooperate in the study and to review the intermediate and final version of this report. All their remarks have been taken into account.

### I. PREFACE AND BACKGROUND

Belgium hosts 25 radiotherapy centers and 11 satellites, which treat about 30,000 patients/year with external photon or electron therapy. On a European scale Belgian centers are small or medium in size. Hadron therapy is not available in Belgium.

An increasing number of hadron therapy centers is being built and operated in Europe, the United States and Japan. In Europe 14 hadron therapy centers are in operation. Five of these are candidate centers for referral of Belgian patients: Orsay / France, PSI / Switzerland, Munich / Germany, Heidelberg / Germany and Pavia / Italy. Another 6 are in a planning stage or under construction and will double the available European capacity in the next 3-5 years. While the USA is rapidly growing in the field of proton beam therapy, Japan is clearly the world leader in carbon ion beam treatment.

Belgium centers send some of their patients with clear indications for hadron therapy abroad. Typically European centers charge between 18,000 and 40,000 €/patient (travelling and lodging excluded). In Japan 40,000 €/patient is being charged but this also includes the follow-up services by the Medical Excellence Japan services. In the USA, where proton therapy is organised on a commercial

basis, an up front payment of the treatment costs of some 100,000 \$/patient is requested. This makes the treatment prohibitive for many Belgian patients.

Sending Belgian patients abroad proves to be rather problematic today because of a variety of obstacles in finding the appropriate centre, in submitting the patient files, in coordinating the logistics including travelling and reimbursement and in organizing the follow-up of the treated patients. Waiting lists, language barriers, travel and lodging costs and social differences make referral even more difficult. This is why in practice only a minute fraction of the eligible patients are presently being sent abroad. A central organisation should be put in place for the coordination of referral and back-referral.

Also in the case of a future Belgian hadron centre, organisation of the referral from all Belgian hospitals to one single centre will be an extremely important topic, since cross-referral is almost inexistent at present. Again here a central organisation will have to determine what type of cancers will be treated. It will also need to guarantee referral and back-referral of all eligible Belgian patients and organise the network that coordinates the clinical and translational research.

Three alternatives were investigated as a future candidate facility for Belgium: 1) A combined centre for irradiation with both proton and carbon ion beams in which one room is equipped with a proton gantry and the other with a fixed carbon ion beam, 2) A two room carbon centre with two fixed beam treatment rooms and 3) A two room proton centre with gantry equipment in both rooms.

The project team of this study provided for a 4th technical alternative (a one-room proton centre), because parallel to this feasibility study, a project to build and operate a one-room proton facility has been started by a group involving IBA, Université Catholique de Louvain, Hôpital Universitaire Saint-Luc and the Région Wallonne. The cost estimates for investment and exploitation in this study vary substantially from the ones that are cited in the UCL project outlines. Due to restricted resources and to a lack of details on the parallel project these discrepancies could not be analysed further.

An expert team composed of the most reputed and representative experts from Germany, Italy, Switzerland, France, the Netherlands and Japan has been asked to discuss on the project content and to deliver a project assessment of this final report. They have participated in 4 expert meetings and gave ample input on project feasibility and critical success factors.

### *1.a. The benefits of hadron therapy explained*

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Hadrons therapy is a generic name for treatment with hadron beams. Hadrons are particles susceptible to nuclear forces ( $\acute{\alpha}\delta\rho\acute{o}\varsigma$  = strong), in practice protons, neutrons or atomic nuclei. This feasibility study of a Belgian Hadron Therapy Centre focuses on two types of hadrons: protons and carbon ions. With these ions, a future BHTC can exploit practically all of the presently known advantages of hadron therapy.

As opposed to hadron therapy, classical radiotherapy, also called photon therapy, departs from highly accelerated electrons to produce an irradiation beam. On hospital level, the required basic equipment is relatively small-sized, financially affordable and has consequently become very widespread over the last decades.

In the more recent developments of hadron therapy however, hadrons are being accelerated to high-energy treatment beams. The nature of these heavier atomic particles is reflected in the substantially larger size, greater technological complexity and higher investment costs.

When compared to state of the art photon therapy, and for a similar dose to the tumour, proton therapy has the advantage of a lower integral dose to the healthy organs surrounding the tumour. It is generally accepted that any reduction of the dose to healthy organs reduces the probability of complications induced by radiation including secondary malignancies.

Compared to the ballistic benefits of proton beams, carbon ion beams have the additional advantage of manifestly higher relative biological efficiency. For the same dose deposition its effectiveness to destroy cancer cells is largely superior. The biological efficiency increases along the trajectory of the carbon ion beam. Healthy tissues are exposed to the less toxic proximal parts while cancerous tissues are hit by the highly toxic terminal parts of the trajectories.

Concurrent to the full report, this summary will successively handle: II. The eligible indications for hadron therapy; III. The number of potential patients for the different indications; IV. The treatment requirements in terms of technical specifications; V. The costs calculations, financing issues and economic considerations; VI. The conclusions and recommendations.

## II. ELIGIBLE INDICATIONS FOR HADRON THERAPY

Hadron therapy started as a side activity in physics research centers. Their clinical activity focused on rare tumours that were difficult to treat because of a dangerous location, often nearby the central nervous system, or on tumours resistance to the standard available photon beams.

In a variety of paediatric cancers for instance, proton therapy is first choice treatment due to its ability to avoid growth and development disturbances, while carbon ion therapy is experimentally used to avoid limb amputation in children with osteosarcoma. These paediatric indications are reimbursed in many countries worldwide.

Although also some indications in adult patients became accepted as standard, they remain restricted to very rare tumours that were the historical niche of clinical activity in physics research centers. Multidisciplinary teams, which were built around the niche, consolidated the excellent results and attracted wide-range referral of patients. This centralization in specialized centers provided the teams with sufficient numbers of patients to conduct clinical research, allowing them to further improve the therapeutic results.

Step by step the above mentioned indications became accepted for reimbursement and are called “standard indications” in the main text of the report. The first proton and carbon ion centers, dedicated to patient treatment were built in the 1990s. During the last decade, many clinical hadron therapy projects have been launched and the worldwide treatment capacity has rapidly increased.

Due to this, another category of indications – called “model indication” in the report – got to be studied. Thanks to progress in medical imaging and computer technology, virtual modelling studies involving hadron therapy were possible since the 1980s. The availability of hadron capacity made it realistic to conduct case studies to test hadron therapy for more common cancers that were identified as good candidates by modelling studies.

These case studies typically focused on subgroups of cancer patients in whom conventional treatment showed disappointing results and for whom new radiotherapy modalities were likely to significantly improve local control or toxicity rates.

Exemplary for model indications are patients with locally advanced unresectable pancreatic cancer treated by carbon ion radiotherapy combined with gemcitabine

that were reported to have a median survival of 24 months. Compared to that, median survival is less than 12 months for a common treatment of photon radiotherapy combined with gemcitabine.

Patients with unresectable locally recurrent rectal cancer who receive photon radiotherapy without or with chemotherapy have a 5-year survival rate of 16% to 27% in the best series. The best carbon ion schedule – with or without chemotherapy - yielded a 42% 5-year survival rate and was associated with less than 5% severe toxicity, well below the expected toxicity from photon radiotherapy ± chemotherapy.

In stage III Non-Small Cell Lung Cancers (NSCLC) proton therapy combined with chemotherapy resulted in a median survival exceeding 2 years as compared to approximately 20 months after photon chemoradiotherapy in the best series. Also here toxicity appears to be diminished.

At least 4 other cancer entities with good anatomical and biological characteristics are being studied in the hadron therapy centers of our expert panel: salivary gland tumours with other than adenoid cystic histology; recurrent head and neck cancer; stage I NSCLC and unresectable hepatocellular carcinoma.

At present, studies of hadron therapy in common cancers do not really substitute photon radiotherapy, mainly because of a lack of capacity worldwide. This might change in the future with increased capacity. Hadron therapy is ready for new directions, like the treatment of oligometastatic disease, which are now explored by advanced photon therapy techniques. The number of model indications is likely to increase in the next years and may finally lead to replacement of photon radiotherapy for a significant proportion of our patients.

### III. THE NUMBER OF POTENTIAL PATIENTS FOR THE DIFFERENT INDICATIONS

For the historically accepted standard indications for hadron therapy this study identified 34-43 children yearly in Belgium. This is a substantially lower number than predicted by the hand-rule of 10 paediatric hadron therapy indications for a population of one million persons.

Table 1. shows that for Belgian adults these standard indications for hadron therapy were identified in 223 patients yearly. Three cancer entities - paranasal tumours, meningiomas and gliomas - contribute to more than two-thirds of the standard indications.

As indicated above, subgroups of patients with common cancers are increasingly being studied in proton and carbon ion therapy centers worldwide. Over the last years, promising results were reported. In the framework of this study 7 model indications were identified corresponding to 1,820 patients yearly in Belgium. Some of the indications, for example stage III NSCLC call for a shift from photon therapy to hadron therapy and would substitute conventional radiation treatment. Other model indications, for example, hepatocellular carcinoma, would represent new indications for radiation therapy.

The selection of the best hadron for each indication is a research topic. Results superior to these expected from the present standard therapy were reported with protons as well as with carbon ions for many indications. The rapid evolution towards the use of few treatment sessions is a strong argument in favour of carbon ion therapy for those indications where proton and carbon ion studies report similar clinical outcome.

Arguably, a Belgian hadron therapy centre should focus on one or a few model indications during the start-up period. Selection criteria for the model indications at start-up should include the feasibility in terms of technical equipment availability and the indication incidence.

Especially the Japanese expert recommended that patients with unfavourable prostate cancer could be considered as model indication suitable for start-up because of the limited technical difficulties and the high patient numbers.

Table 1.: Estimates of adult patients with standard or model indications eligible for hadron therapy in Belgium per annum.

No.	Indication	Type of hadron therapy	Estimates of eligible patients (n)
	<b>Standard</b>		
1	Chordoma (all stages & sites)		
	Skull base	Carbon ions Protons	2
	Sacral & coccygeal	Carbon ions Protons	3
	Paraspinal	Protons	1
2	Chondrosarcoma (all stages & sites)		
	Skull base	Carbon ions Protons	1
	Sacral & coccygeal	Carbon ions Protons	2
	Paraspinal	Protons	1
3	Bone & soft-tissue sarcoma (all stages of skull base, paraspinal, sacral & coccygeal)	Carbon ions Protons	24
4	Malignant melanoma of the upper aerodigestive tract	Carbon ions	8
5	Adenoid cystic carcinoma of head & neck (all stages)	Carbon ions	21
6	Paranasal tumours (all stages)	Protons	65
7	Meningioma benign and malignant	Protons	24
8	Low-grade glioma (grade 1 & 2)	Protons	71
		<b>Carbon ions</b>	<b>61</b>
		<b>Protons</b>	<b>162</b>
	<b>Model</b>		
9	Pancreatic cancer (all stages)		
	Locally advanced inoperable	Carbon ions	401
10	Rectal cancer (primary & recurrent)		
	Local recurrence	Carbon ions	82
11	NSCLC (stage III)	Protons	588
12	Major salivary gland tumours other than adenoid cystic carcinoma (all stages)	Carbon ions	50
13	Head & neck cancer (primary & recurrent)		
	Re-irradiation	Protons	156
14	NSCLC (stage I)	Carbon ions	179
15	Hepatocellular carcinoma (all stages)		
	Primary & recurrent size <3 cm: adjacent to vessels or bile ducts or the gastrointestinal tract;	Carbon ions	364
	Primary & recurrent size >3 cm		
		<b>Carbon ions</b>	<b>1,076</b>
		<b>Protons</b>	<b>744</b>
	<b>All indications</b>	<b>Carbon ions</b>	<b>1,137</b>
		<b>Protons</b>	<b>906</b>

Considering its lack of a physics research centre with a track record of hadron therapy, Belgium will have to rely on commercially available equipment as a start-up platform for hadron therapy.

Analysis of the beam requirements for model indications reveals that only indications 10, 12 and 13 of the above mentioned table could be done with today's commercially available equipment (see section IV). In a combined centre this first platform would treat some 550 patients/year.

For the other model indications, representing some 1530 patients/year, additional and more fundamental research and development in new equipment (a gantry for carbon beams for instance) and in clinical development (mainly technology to position and treat moving tumours) is required. It is likely that technology to treat moving tumours will become available in the next 2 to 3 years.

## IV. THE TREATMENT REQUIREMENTS IN TERMS OF TECHNICAL SPECIFICATIONS

### *4.a. Hadron therapy related to new developments in photon therapy*

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The recent innovations in conventional photon radiation have offered new possibilities for reducing toxicity and increasing cure rates. But do they narrow the gap with hadron therapy or does hadron therapy evolve in a similar way?

The study analyses the developments over the last 2 decades in radiation therapy. Integration of two- and three-dimensional imaging techniques with the treatment machines in the late 1980s formed the basis of image-guided patient positioning which matured to various forms of image-guided radiation therapy (IGRT). Practical devices to define the shape and modulate the intensity profiles of photon beams were developed since the early 1990s and formed the basis for intensity-modulated radiation therapy (IMRT).

The concept of radiation therapy planning based on functional imaging, which gives information of radio-resistance inside tumours and tissues, was launched in the early 2,000. IGRT, IMRT and functional imaging formed the foundations for further developments.

Stereotactic body radiation therapy (SBRT), the irradiation of targets anywhere in the body with stereotactic precision became possible by combining IGRT and IMRT techniques. For small-sized tumours, SBRT opened the possibility to deliver high doses in a single or a few radiation sessions safely with IGRT and IMRT techniques securing precise dose delivery and tightly shaped dose distributions, respectively.

Dose painting, the delivery of dose distributions, which are tailored to intra-tumour

variations of radio-resistance, was made possible by combining functional imaging with IMRT techniques.

Contemporary research aims at adapting the daily treatment to changes in anatomy and biology that occur during the course of radiotherapy. This approach is called adaptive radiation therapy (ART). ART involves recursive use of IGRT, IMRT and functional imaging techniques.

Each of these developments however is also applicable to hadron therapy and is being implemented there, though at a slower pace than in photon therapy. Apparently there is no real risk that hadron therapy will definitively lose its advantage over evolving photon therapy.

#### *4.b. Sources of information*

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Sources of information were meetings on hadron therapy and visits to the centers in Germany (Darmstadt, Heidelberg), France (Orsay), Switzerland (Villingen), Italy (Trento, Pavia) participation in European hadron projects and attendance in ESTRO hadron teaching courses.

Technical specifications, layout and equipment characteristics were discussed in four expert meetings that took place in Brussels.

Brief discussion with company representatives (IBA, Belgium; Still River/Mevion, US; Varian, US; Sumitomo, Japan) took place at the ESTRO Hadron Therapy Teaching Course in March 2012.

#### *4.c. General concept*

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The general facility concept is a centre of a minimum size offering the possibility to treat Belgian patients that are eligible for hadron therapy.

The choice for proton or carbon still remaining open in the feasibility study, the experts advised to consider 3 types of facilities: combined proton and carbon ions, proton only and carbon ions only. They argued unanimously to install at least 2 treatment rooms from the start of clinical operations to allow continuity of clinical operations during maintenance or upgrades.

The start of the UCL project parallel to this feasibility study has been the main motivation to accept a 4<sup>th</sup> technical variant in the study: that of a single room proton centre, although the experts argued strongly against a one-room facility as a starting basis for a Belgian hadron therapy project. The main argument against is the difficulty to provide continuous clinical operation. Maintenance and upgrades in the treatment room carry risk of halting clinical operations. The one-room facility

may become rapidly outdated under the pressure of keeping the facility unchanged in order to pursue continuity of clinical operations.

It is the unanimous opinion of the experts that a BHTC should be hospital-based. The competence of a general hospital is needed for anaesthesia, surgery, imaging and general patient care in order to concentrate on acquiring hadron treatment experience that is not present in Belgium today. The centre's mission of education, research and development calls for the services of an academic hospital. In view of its relatively small Belgian population of 10.5 million inhabitants and its strong dependence on commercial vendors, one single centre is strongly favoured

Of the present day commercial vendors, Varian and Still River/Mevion restrict themselves to proton therapy. IBA and Sumitomo would accept to compete in carbon ion projects. Sumitomo and Hitachi have build proton therapy facilities. Toshiba builds carbon ion therapy facilities. Mitsubishi builds facilities for treatment with both ions. According to our Japanese expert however all 4 Japanese vendors would eventually be capable to build any type of facility since they all participated in and have access to the combined proton/carbon HIMAC project of the National Institute of Radiological Sciences.

Because of restricted resources, elaborating detailed layout plans could not be part of the first phase of the feasibility study. The experts were clear: make the patient flow the determining factor in the layout. The footprint, preliminarily estimated on a square of 60 to 70 m by 60 to 70 m, will ultimately depend on choices made: gantry or fixed beam, type of accelerator and 1 or 2 accelerators for the combined proton C ions facility.

#### *4.d. Clinical informatics, interfaces and networking*

Major developments take place in the domain of Record and Verify systems in photon radiotherapy. They support the clinical management and provide the interfaces with hospital information systems as well as the networking between the equipment used in treatment preparation, in treatment delivery and in quality control. Interfacing with the hospital informatics systems still remains a challenge at the present stage of development. In hadron facilities these developments appear to lag behind, jeopardized the start-up of operations in newly constructed centers. Our experts agreed that photon therapy technology should be the reference for designing Record and Verify systems in a future hadron therapy centre and that vendors should be questioned on that basis. The investment cost of a clinical information support system is estimated at 500,000 Euros. The cost of

the logistic facilities and offices would be approximately 2.5 million Euros for the 2-room scenarios and at 1.0 million Euros for the 1-room scenario.

#### *4.e. Beam availability and uptime*

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Beam availability for clinical treatment determines the operating schedule of the facility and is a main factor in efficiency during clinical operation. Hadron therapy installations are very reliable. Clinical operation of 16 hours/day, 6 days/week is feasible.

Hadron therapy installations usually have a single accelerator. When the beam is directed to one room, another room may have to wait for beam. Beam splitting technology is under development to enable simultaneous irradiation in different rooms.

#### *4.f. Beam direction specification*

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Photon radiation uses a beam direction that can turn the beam in all directions around the patients. This technological equipment, called gantry, has become standard also in proton therapy rooms. No commercial vendor offers a gantry for carbon ions. Only the Japanese vendors are planning to develop one.

Fixed beam directions in carbon treatment being the only commercially available equipment, the experts believe that inclined beams might extend the range of indications of a purely horizontal beam.

A key-request for modern efficiency of 3D-set-up imaging is a serious concern for hadron therapy. Patient couches must have the operational characteristics of a modern photon couch. Considering the limitations of fixed beams, the ideal positioner design needs further investigation.

Investment costs estimations of this study are based on the assumption of one proton gantry and a horizontal fixed beam for the combined scenario, 2 horizontal fixed beams for the C ions scenario, 2 gantries for the proton only scenario. The reference one-room proton scenario hosts a gantry.

#### *4.g. Beam characteristics*

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The maximum cross-sectional size of the planning target and the depth that must be covered are important parameters to specify the cross-sectional beam size and the energy range. Given the assumption of a single hadron therapy centre, no compromises have been assumed on the range of the eligible indications for

hadron therapy as described under II. For C ions, the minimum specifications commonly used for protons should be used as reference for negotiations with the vendors.

Pencil beam scanning and fast re-scanning will have to be requested and discussed with potential vendors. The accelerator, beam lines and all treatment devices must be configured in order to treat with up to 230 MeV/nucleon for protons and to 400 MeV/nucleon for carbon beams.

#### 4.h. Treatment preparation, set-up and correction

This section involves immobilisation and set-up techniques, imaging for planning, plan verification, set-up imaging in-room and remote, set-up correction, per-treatment monitoring. It should be part of a later phase of the feasibility study.

#### 4.i. Investment costs overview

The table 2. below defines the investment costs for the different technical scenarios that have been used in the costing models (see further).

Table 2.: Investment cost (€).

Investments	C ion	Proton	Combined	One-room proton
	Excl. VAT	Excl. VAT	Excl. VAT	Excl. VAT
Building	25,000,000	15,000,000	30,000,000	10,000,000
Equipment	50,000,000	25,000,000	60,000,000	20,000,000
Imaging	4,000,000	4,000,000	4,000,000	2,000,000
Simulation	2,000,000	2,000,000	2,000,000	1,000,000
Planning	1,000,000	1,000,000	1,000,000	1,000,000
Record & verify	500,000	500,000	500,000	500,000
Anaesthesia	0	1,500,000	1,500,000	1,500,000
Facilities	2,500,000	2,500,000	2,500,000	1,000,000
<b>Total investments</b>	<b>85,000,000</b>	<b>51,500,000</b>	<b>101,500,000</b>	<b>37,000,000</b>

## V. COSTS CALCULATIONS, FINANCING ISSUES AND ECONOMIC CONSIDERATIONS

### *5.a. Cost calculation and financing issues*

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#### I. Context and introduction

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Reimbursements of approximately 18,000 to 40,000 €/patient are commonly charged for hadron treatments in European and Japanese centers (in Japanese rather 40,000 € including logistic services). Our first calculations revealed that these amounts are far from sufficient to cover the calculated full costs. This observation led to the hypothesis that European and Japanese centers have other financial resources than mere patient reimbursement at their disposal.

Discussions with the expert team confirmed that and made the BHTC team realise that the majority of the projects in surrounding countries, to which a potential Belgian centre would have to benchmark, were started as research and development projects both in the field of clinical and technological development. Public means were often devoted to these projects as an up front investment, hence not accounted for in the reimbursement of the - purely operational - treatment costs.

American centers are typically set on a commercial basis and have to take the full range of costs for capital and risks into account for their reimbursement setting. It is therefore not surprising that some of these centers are known to charge 100,000\$ per patient or more.

These very distinct backgrounds and approaches made us decide to perform the cost calculation for this project in different ways (business model vs. Activity-Based Costing model) and to consider different financing models (private, public and mixed financing).

The business model calculation evaluates the financial implications of setting up a facility over time. Such an approach analyses the costs incurred from the phase of preparation, first investment and commissioning, over the years where the centre starts to accrue patients until operation at full capacity and beyond.

Different financing models - private, public and mixed – were considered setting the reimbursement at a level required to make the centre sustainable.

Sensitivity analyses provided insight in the consequences of longer commissioning periods, of different interest rates, higher investment costs and lower personnel requirements. The latter two have been instigated by the comments of the experts who felt that in our literature-based input parameters the investment costs might be underestimated and the personnel requirements rather overestimated.

The Activity-Based Costing (ABC) model was used to analyse the departmental and treatment costs for a centre in a specific year corresponding to “steady state operation”. Annual operational costs and average cost per patient were benchmarked to the data obtained in the business model for centers in full operation.

The ABC model proved to be specifically useful for computing treatment-specific costs per type of indication. This was done for private as well as public financing. Sensitivity analyses focused on the impact of variable investment costs, different product mixes and the impact of fractionation on the treatment cost. Furthermore, the ABC-model was used to evaluate the productivity of different personnel categories, all included or not taking research and development into account. Calculations were all performed using the public financing model for a combined centre, except for the analysis on personnel productivity, where all technical scenarios were evaluated.

## II. Technical alternatives

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Combined centre:

The basic technical solution is based on a minimal but necessary equipment for both proton and carbon therapy. The centre consists of one or two accelerators, two treatment rooms and the ancillary equipment consisting mainly of imaging, simulation, planning, record & verify and anaesthesia equipment.

Two room carbon centre:

The number of adult patients that might profit from carbon therapy is potentially very large, so that a carbon only centre is a promising alternative to the combined centre. The pure carbon centre consists of one accelerator, two fixed beam treatment rooms and the ancillary equipment, consisting of imaging, simulation, planning and record & verify. The anaesthesia facilities can be omitted, as no paediatric patients will be treated.

Two room proton centre:

A 2-room proton centre would be today's technically safer solution. It would be equipped with one accelerator and would have 2 treatment rooms, both with

complete gantry equipment. Furthermore, there would be a similar set-up of the ancillary equipment as in the first alternative.

#### Single room proton centre

Contrary to the above alternative, the single room proton centre has been reduced to the bare minimum that might still fit the Belgian stand-alone hospital in terms of bearable investment costs. Only a single treatment room would be provided, together with its accelerator. The investment of the ancillary equipment can be reduced due to the insertion of the proton centre into an established photon radiotherapy department.

### III. Input parameters

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The input parameters include building and equipment investment (see earlier) and financing costs of amortization, personnel costs, maintenance costs, energy costs, facility management costs, medical consumable costs and insurances. Some costs have been purposely omitted from the model: costs for the lands (considered to be available from the hospital site where the hadron centre is operational) and demolition costs of the equipment and building at their life end. All cost simulations however were designed to provide for sufficient cash flow at the end of the amortization period (years 16 to 20 after start-up).

For the baseline parameters used in the modelling, the KCE report vol. 67A, published in 2007, was taken as starting point and reference [KCE report 2007]. They were however adapted to conform to the actual state of the art based on discussions with the experts and literature review.

Most important adaptations were made in investment costs, in personnel requirements and in the building's maintenance costs. In order to facilitate the reading of this summary, for the choice of the many input parameters and for the methodological details - important as they may be - we have to refer to the complete report.

### IV. Financial Models

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#### ■ 1. Description of the assumptions of the business model

In the business model, the treatment costs have been modelled for 12 cases (4 technical alternatives times 3 financing methods). Each model case contains an overview of the investments, operational characteristics, exploitation costs, annuities, cash flow and required reimbursement rates for a certain model.

Investment expenditures have been spread over a project preparation and commissioning period of 4 years. During this period, a fraction of the personnel has already been provided for training, preparation and commissioning.

The operational parameters include the yearly organisation and workload, staffing costs and number of patients of the centre. We assumed to operate all technical alternatives at full capacity 4 years after commissioning, which is 8 years after initial project start.

An average and fixed reimbursement rate per patient has been determined for each case at full capacity. In all technical alternatives the reimbursement rate has been fixed at a level where positive cumulated net cash flow is generated 16 years after the start-up. At that time, the accumulated reimbursements have become large enough to balance the total cash out flow, including investment and operational expenditures, bank repayments including interest payments and short-term loans and their interests. A yearly interest rate of 5% on both long- and short-term loans has been assumed.

## ■ 2. Financing methods

In the case of private financing the entire cost coverage for setting up the centre has been obtained through private financing. The basic investment costs, the personnel expenses during commissioning and the interim interests on the investment capital required during this period have been considered to be part of the initial capital that has to be financed.

From start-up another 4 years have been planned to ramp-up to full patient treatment throughput. With the assumption that the RIZIV-INAMI only reimburses in proportion to the number of patients, a cash drain has to be financed separately during this ramp-up period and thereafter, with short or medium term private loans. The required reimbursement rate per patient has thus been defined at a level such that the Net Cash Flow situation becomes positive in a reasonable period of time. In the modelling this supposed to happen at year 16 after starting the treatment of the first patient (and thus shortly before the end of the amortization period of 20 years).

In the mixed financing model it has been assumed that 40% of the funding comes from private funding and that the remaining 60% has been covered by public funding. Hence, the same assumptions hold here as for private financing, except that public financing has been supposed to take 60% of the investment costs out of the project and thereby reduce the annuities by 60%.

In the calculation with public financing, the full investment costs as well as the personnel costs during commissioning have been taken out of the project. Hence, the calculation has been based purely on the operational costs, which are the same as for the other financing solutions (e.g. the maintenance costs are of course independent from the source of the investment financing). Apart from that, modelling remains identical as in the previous financing methods.

### 3. Results

The yearly operational costs in € of the 4 technical solutions with the 3 financing models at full capacity utilisation are given in table 3 below (inflation not taken account of).

Table 3.: Yearly operational costs (€).

	Different technical solutions			
	Combined centre	Carbon only centre	2-Room proton centre	Single room proton centre
Private financing	24,800,826 (12,008,412)	22,382,063 (10,177,104)	16,451,459 (6,406,537)	10,587,015 (4,691,272)
Mixed financing	17,595,779 (4,803,364)	16,275,801 (4,070,841)	12,607,536 (2,562,614)	7,772,251 (1,876,509)
Public financing	12,792,414 (0)	12,204,959 (0)	10,044,922 (0)	5,895,742 (0)

These operational costs include annuities, personnel, maintenance, energy, facility management, medical equipment and insurance costs. Yearly annuities have been put between brackets because of their important impact.

The average reimbursement levels that have to be foreseen in order to cover the total of operational costs, and thereby making the centers sustainable for 4 technical solutions and 3 financing methods, are given in the next table 4.

Table 4.: Required reimbursement rate (in € per patient).

	Combined centre	Carbon only centre	2-room proton centre	Single room proton centre
Patients treated / year	534	760	355	165
Private financing	51,150	32,400	51,200	70,600
Mixed financing	37,000	24,000	39,900	52,900
Public financing	27,550	18,400	32,300	40,950

The number of patients that can be treated highly depends on the number of fractions required for the different indications. For carbon ion treatment an average of 15 fractions is put forward, while for proton treatments 30 fractions have been assumed. This explains why a carbon only centre can treat much more patients than a two-room proton centre. In addition the latter also treats paediatric patients that require the longest treatment time.

This decisive element, together with the high impact of the required investment on costs - being the highest for carbon ion equipment - roughly explain the tendencies for required reimbursement rates in the table above.

#### ■ 4. Sensitivity analysis

##### *Delay in commissioning or ramp-up.*

The required reimbursement rate is very sensitive for delays in commissioning and ramp-up in the case of a private financing of a combined centre. Every year of delay roughly adds 5,000 €/patient to the required reimbursement rate. In the case of mixed financing, this effect is about two-thirds of it. This effect of course becomes almost negligible in public financing because the initial debts at start are inexistent. The risk of delayed start-up highlights the need for public financing.

##### *Long-term interests.*

Every extra 2% long-term interest on the privately financed capital adds about 4,000 €/patient to the required reimbursement. In the case of mixed financing, this effect is about half of that. This effect evidently disappears with public financing.

##### *Investment costs.*

The impact of the investment costs is evidently important by the nature of these large investment projects. Whatever technical choice is made, investment costs make up roughly 50 % of the treatment costs when the project has to be privately financed. In the discussions with the experts, no firm data could be gathered on investment costs. Instead their advice has been to start contacting the vendor in a next stage of the feasibility study. Some of the experts cited investment costs in hadron projects (especially for carbon equipment) that were twice as high as our estimation, whereas other stated that part of our estimates were too high. Obviously this risk cannot be whipped away by public financing, but will be carried instead by the involved community.

##### *Personnel requirements and costs.*

The expert team felt that, especially for the proton centers, the personnel numbers seemed to be overestimated. Hence, an estimated decrease of 30% of the

personnel requirements was analysed. It showed that such a decrease in personnel costs impacts on treatment costs for +/- 8% in case of private financing; for approximately 10 % for mixed financing; and 12 to 25% in case of public financing. Although this impact is certainly not to be neglected, it however does not affect the major conclusion of this study.

The ABC-model gave insight into the productivity of the personnel, which showed insufficient occupation for some personnel types. This however gives space for the clinical research tasks that will probably have to become a standard part of the activities. Conversely, if research personnel costs can be covered by other sources than the treatment reimbursements, this would have a favourable impact of approximately 10% on treatment costs.

Higher personnel costs as pinpointed by the KCE proved to have a rather small impact on the yearly operational costs.

#### *Operating scenarios and product mixes.*

The sensitivity of the treatment cost per patient was demonstrated in the ABC calculations to be most dramatic when reducing the number of fractions per patient. If the base case adult treatment cost with carbon ion for 15 fractions amounts to 21,507 € in a combined centre and public financing, hypo-fractionation to 4 fractions (as is experimented with in Japan) brings down the cost to 9,320 €/patient.

### *5.b. Health economic considerations*

Because of the reported favorable balance between costs and outcome of proton treatment in childhood cancer, it was decided not to focus on this clinical example in the health economic evaluations. Along the same line, other indications defined as 'standard' were not withheld either for health economic evaluation, as it seemed more worthwhile to focus on the 'model' indications. Not only do these indications represent the vast majority of the population mix of a potential hadron centre, their value for money is also the most uncertain as well as critically related to the balance between expected gain in outcome and patient selection. From the 7 model indications eligible for hadron therapy (see II) the following three were selected as representative for a cost effectiveness analysis: locally advanced pancreatic cancer; locally-advanced non small cell lung cancer and unresectable hepatocellular carcinoma.

Due to the unavoidable parallel and iterative progress in different modules of this project, the selection of these indications occurred prior to the formulated conclusions and recommendations for a first phase technological choice of a Belgian centre. In light of this, the indications selected for the health economic evaluation

may currently seem less relevant. It is expected however that in the rapidly evolving technological landscape, the required technical specificities to treat these indications will be available by the time of an operating hadron centre in Belgium.

For details on the data, the methodology and the outcome of this cost effectiveness study, we refer to the main report. Here we will only sketch the general results of the efforts made and the further steps to be taken.

Overall the health economic evaluations show that hadron therapy is borderline cost-effective compared to the best available treatments, with a cost-effectiveness ratio of around 30,000 € to gain one Quality Adjusted Life Year (QALY) in most indications. In terms of cost per Life Year (LY) gained calculations show outcomes of approximately 20,000 € per year gained by hadron therapy.

The above results were obtained with hadron costs calculated in the context of public financing. The scenario analyses exposed that with private financing the cost-effectiveness of hadron therapy would exceed the commonly accepted threshold of 30,000€-40,000€/QALY of cost-effective care in Belgium. The steering committee of the BHTC feasibility study moreover pointed out that the photon therapy costs used in the analyses, derived from the recently published KCE report 198 on radiotherapy costs in Belgium, are more in line with mixed financing. It was therefore requested that the health economic evaluations would also be performed for a centre with mixed financing. It is proposed that this would become part of a second phase of the feasibility study.

Apart from the high sensitivity to the treatment costs, the results were also found sensitive to the effect of hadron therapy on disease control and quality of life.

Fine-tuning the cost and outcome parameters requires more details of the technical scenario and related investment costs as well as further clinical research to allow more stable and reliable cost-effectiveness statements. The same holds for the definition of correct treatment comparators for the patient population treated with hadron therapy. These issues can be looked at in more detail in a second phase of the feasibility study.

## 5.c. Conclusions

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### I. Cost calculations and financing issues

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The benchmark cost of approximately 18,000 to 40,000 €/patient, commonly charged for hadron treatments in Europe, is mostly insufficient to cover the calculated full costs.

A two-room carbon ion centre is the most attractive in terms of cost per treatment, consequence of the higher patient throughput due to lower fraction numbers per treatment and omission of the more time-consuming paediatric patients.

Proton treatments are most costly in all technical solutions. This is in line with the higher number of fractions and the higher treatment time requirements for paediatric patients.

All factors that allow reducing the total treatment time positively influence the ultimate costs. The current clinical interest for shorter fractionation schedules, especially in carbon ion treatments, may further translate into more favourable economic scenarios.

Treatments delivered in a combined centre are typically more expensive than the same treatment delivered in dedicated proton or carbon ion centers of the same size.

Public financing seems to be the only viable financial option, as private financing would require excessive reimbursement rates.

Uncertainties in required commissioning time and in investment costs all point away from the practical feasibility of private investment in this times where banks are reluctant to take any risks.

Personnel requirements are not yet well established and need further refinement depending on the technical solution and the associated patient through-put.

In line with the reality of a high-tech environment as a hadron centre, clinical and technological research and development should be integrated part of the activities.

### II. Health economic evaluation

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Based on the assumptions of the calculated models, the health economic evaluations show that for most indications hadron therapy is borderline cost-effective

compared to the best available treatments at a cost of roughly 30,000 € per Quality Adjusted Life Year (QALY). This is a commonly accepted threshold for cost-effective care in Belgium. In terms of cost per Life Year (LY) gained calculations show outcomes of approximately 20,000 € per year gained by hadron therapy.

These results were obtained in the context of public financing. It was demonstrated that they are highly sensitive to the overall costs per treatment as well as to the effect of hadron therapy on disease control and quality of life.

Due to the observed uncertainties, so far no decisive conclusions can be drawn from the economic evaluations. Further in-depth clinical studies and economic calculations are required to allow more stable and reliable cost effectiveness statements relevant to the project. The scenario of mixed financing of the initial investment has to be calculated and assessed in a second phase of the feasibility study.

## VI. THE CONCLUSIONS AND RECOMMENDATIONS

### *6.a. Conclusions*

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The most critically interrelated findings and statements from the different sub-modules are reviewed here in order to come to some conclusions and recommendations. It is indeed necessary to align these related findings and to bring their relationship to evidence. Risk containment for a potential Belgian Hadron Centre should be central in this reasoning.

The following important risks were identified for this high investment project:

- technological risks (some equipment still being an ongoing development)
- investment cost risks (some equipment still not commercially available making investment costs difficult to estimate)
- clinical research risks (some indications requiring further clinical research)
- all leading consequently to cost control risks of the project and of the required reimbursements rates.

Number of potential Belgian patients

1. According to conservative estimations based on the Belgian Cancer Registry, the numbers of patients/year with generally accepted (standard) indications are 223 for adults and 34 for children.
2. Constructing a Belgian centre to treat only commonly accepted (standard) indications would technologically be the safest - because relying on commercially available technology (see below) – but at the same time very expensive due to the fact that the total number of patients is too small.

3. Research on treating more so-called model indications of more common cancers, has only been started recently, as more hadron beam capacity became available worldwide. For today's 7 most convincing (model) indications of this category, 1,820 Belgian patients/year were identified.
4. Part of these model indications can be treated with commercially available technology, the other part requiring further equipment development (see later).

#### Technical solutions and technological feasibility

1. Budgetary leanness and commercial availability were assumed in the study by opting for a minimal size facility (2 treatment rooms) at the start-up. Investment cost risks should be limited, but the installation should be designed to allow for further expansion and development.
2. A combined proton/carbon ion beam centre is the only solution that is conceptually capable of treating all indications on the long run (see above).
3. Belgium relies on vendors for a hadron centre and cannot count on large competence centers for technological development of hadron equipment.
4. It is important also to make a distinction between commercially installed technology - as opposed to technology developed by research and development programs in pioneering hadron therapy centers - in relation to the treatable indications. Commercially available technology can treat the generally accepted standard indications but not all of the more common cancer model indications that were identified in this study.
5. Commercially available technology would enable treatment of 3 of the last category indications. These common cancer indications are locally recurrent rectal cancer, non-adenoid cystic major salivary gland tumours and re-irradiation for head and neck cancer.
6. The treatment of other common cancer model indications however requires additional technology for treatment: other than horizontal beam directions for carbon ions, technology to treat moving tumour sites and three-dimensional imaging for precise positioning. Companies make large efforts to turn the technological developments of the pioneering centers into commercial products but the timescale of availability and the cost of the products remain uncertain.
7. Therefore all cost simulations in this study were based on commercially installed technology: fixed horizontal beams for carbon ion therapy rooms and gantries for proton therapy rooms.

Economic and financing issues, cost simulations and reimbursement.

1. The benchmark for hadron treatment of approximately 18,000 to 40,000 €/patient, commonly charged for hadron treatments in European and Japanese centers, will also hold for Belgium.
2. Such reimbursement level however appears to be insufficient to cover the calculated full costs of a Belgian centre when privately financed.
3. Public financing seems to be the only viable financial option, as private financing would require too high reimbursements.
4. Also the risks of prolonged commissioning as well as uncertainties in the investment costs make a private financing approach to date unrealistic and unfeasible.
5. In line with the reality of a high-tech environment as a hadron centre, clinical research should be an integrated part of the activity.
6. Our calculations suggest that of the 4 presented technical solutions, a two-room carbon ion centre is financially the most attractive in terms of cost per treatment, consequence of the lower number of fractions delivered per treatment.
7. A combined centre though is favoured because it assures treatment of all eligible indications on the long run (see above).
8. All factors that allow reducing the total treatment time influence the ultimate cost. It will therefore be of utmost importance to optimise the operational procedures and to pursue the clinical research in hypofractionation (less fractions per treatment).
9. All performed health economic evaluations show that hadron therapy is borderline cost-effective compared to the current standard of care. However, in all analyses, the sensitivity to the cost and the clinical outcome of hadron therapy, as well as the heterogeneity in patient populations treated, underscore that to date no decisive conclusions can be drawn from these health economic evaluations.

## *6.b. Recommendations*

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### *I. Regarding a Belgian hadron therapy centre*

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#### 1. The location, organisation and management

1. We recommend building a single centre at a single site being the campus of a large general hospital that can provide the complementary medical services: medical imaging, oncologic care services for children

and adults, day clinic, hospitalization, surgery, emergency medicine and anaesthesia. Due to the fact that hadron therapy implies a strong research program (medical, technology and biology) an academic hospital should be preferred to a non-academic hospital.

2. We recommend an independent organization and management structure for the future Belgian hadron therapy centre. The collaboration with the hospital(s) that provide complementary services can be secured through service liability agreements.

## ■ 2. The technical aspects

1. Only a centre that offers proton and carbon ion therapy could cover all clinical indications. We therefore recommend reducing the 4 technical scenarios of the feasibility study to a single one: a centre that allows treating with protons and carbon ions, further called (p+C)-centre.
2. We recommend a flexible design for the future (p+C)-centre that allows treating all standard indications as well as the least challenging model indications from the start of operations. The design must foresee the possibilities of expansions and technological upgrades required for treating the more challenging model indications in a second stage.
3. A strong disagreement exists between the Japanese and European experts regarding the technological concept of a (p+C)-centre. We recommend a pragmatic approach of accepting the solution that is favoured by the ultimately selected equipment companies.
4. We recommend a limited exploratory consultation of the potential hadron therapy vendors IBA, Mitsubishi, Toshiba and Sumitomo to i) obtain information on the status of technologies in development, ii) identify opportunities for participation in their research and development and iii) assess the cost involved.
5. Based on the clinical objectives regarding the coverage of indications, we recommend making a precise description - together with each company - of the equipment that would be needed both inside and outside the treatment rooms and what building and layout is required. On the basis of that a more precise investment cost estimate can be made which would reduce the uncertainty range that has been applied in the sensitivity analyses of cost- and cost-effectiveness studies during phase-I of the feasibility study.

### ■ 3. Evolution of the start-up platform

Extension of the clinical activity to more ambitious model indications will require additional investments to cover upgrades of the installation and a further research, development and implementation program.

## II Regarding access for Belgian patients to hadron therapy

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A yearly recurrent budget of more than 3.5 million Euros is being retained from the Cancer Plan to ensure that Belgian patients would have access to hadron therapy in foreign countries. In almost 4 years, not a single Euro of these recurrent budgets has been used. In spite of a visionary political decision and the reservation of this budget, the situation for the patients who need hadron therapy has deteriorated. Uncertainties in reimbursement and unreasonable delays in refunding the costs of travel and lodging during treatment have turned hadron therapy into a therapeutic option for patients from the higher socio-economic classes only. We are convinced that this reality is quite the opposite of what the Cancer Plan intended.

We therefore recommend that:

1. The budget should be made immediately accessible for referring patients.
2. Following priority ranking should be used: 1. Paediatric standard indications; 2. Standard indications in adults; 3. Model indications according to the table (priority ranked top to bottom) in Submodule 1.
3. 95% of the yearly budget would be used for covering the direct patient-related cost and 5% to cover the cost of a Central Liaison Office.
4. This Central Liaison Office supports logistics and organizes travel, lodging and follow-up for eligible patients.
5. For example, the Foundation against Cancer or another existing Belgian organization with a long track record of covering the multi-dimensional aspects of helping cancer may become the Central Liaison Office in a very short time.
6. The privileged relations with the foreign experts during this study are used to facilitate referral. Their centers in Europe and Japan are willing to accept all Belgian patients with paediatric and adult standard indications. The team of this feasibility study could attempt getting access for Belgian patients also for the missing model indication.
7. The Central Liaison Office would also help the integration of a future Belgian hadron therapy centre in the existing network of centers. Like other facilities worldwide, the future Belgian centre will have to focus on a limited number of indications. For these indications, the

Central Liaison Office could organize the path of care through the Belgian centre while for other indications it would still pass through foreign centers. Hence, we recommend continuing the financing of the Central Liaison Office after a Belgian hadron therapy centre has started clinical operations.

### III. Limitations of the feasibility study

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1. At the start of the feasibility study, the questions focused on the number of eligible patients in Belgium, on cost, on cost-efficiency and on alternatives for hadron therapy in the rapidly evolving oncological scene.
2. As soon as the arguments in favor of a Belgian hadron therapy center became stronger, the Steering Committee started asking questions of direct importance for building a hadron therapy centre in Belgium:
  - a. Containment of the uncertainties on investment costs
  - b. Implantation site
  - c. Organization structure
  - d. Financial structure
  - e. Scope including research
  - f. Training of staff
  - g. Organizing referral
  - h. Collaboration with the Walloon one-room proton centre
3. The group behind the Feasibility Study was limited in its possibilities to address these questions. Some of the answer will certainly depend on the association that will finally build and exploit the Belgian hadron therapy centre. Therefore this group can only give a recommendation on how to address these key questions (see below: Declaration of intent to dialogue with the public authorities).

### IV. Proposal for phase 2 of the feasibility study

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1. We recommend the preparation of a “Declaration of Intent to dialogue with the public authorities”. This would constitute an open call in which the public authorities organize a dialogue with parties that are interested to develop a MasterPlan that must lead to a Belgian Hadron Therapy centre. The feasibility study serves as the 'cahier de charges' regarding the services that the Centre should provide to society.
2. The Declaration of Intent should be brief, but still contain following topics:
  - a. Description of the interested party
  - b. Proposal regarding the implantation site
  - c. Vision regarding organization and financial structure

- d. Vision regarding research and training of staff
  - e. Vision regarding referral and collaboration
    - i. At the local, regional, national and international levels
    - ii. Possibly also with other hadron therapy initiatives in Belgium
3. The Steering Committee could also play a role in the dialogue and help identifying the parties that are eligible to develop a MasterPlan.