Sundhedsstyrelsen
Danish Health and Medicines Authority

# The establishment of a national center for particle radiotherapy in Denmark

## Contents




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## Summary in English

Proton radiotherapy uses charged particles to deliver precision high-energy beams of particles to destroy cancer cells, and seems particularly suitable for childhood cancers, as there is a potential to reduce side-effects such as secondary cancers. The increase in potential demand as well as the rising costs of treating patients abroad and the requirements to treat malignant disease in a timely fashion, underscores the need to establish a national center for particle radiotherapy in Denmark.

At the request of the Danish Ministry of Health, a technical assessment on the establishment of one, single national Danish center has been carried out by the Danish Health and Medicines Authority aided by an international panel of experts in the field.

Joint bids were received from two consortia: One proposal is to place the center adjacent to the Royal Hospital (Rigshospitalet) in Copenhagen; this proposal was submitted by the hospital, the University of Copenhagen and the Capital Region. The other proposal is for a national center for particle radiotherapy integrated into the new university hospital being constructed in Skejby outside of Aarhus; this application was submitted by the hospital, the University of Aarhus and the Region of Central Denmark.

The Copenhagen group proposes a compact proton therapy facility solution. It is argued that proton delivery technologies have advanced considerably, and compact solutions have matured. A single room compact proton facility would be placed in a new small building as an extension to the existing Department of Radiotherapy at Rigshospitalet, with the aim of being able to treat 450 patients annually from the first year, ramping up to 900 patients annually.

The proposal for a national center for particle radiotherapy in Aarhus envisages using commercially available technical solutions to match the overall vision and strategy for the national center to be built on a building plot next to the Department of Oncology at the new Aarhus University Hospital. The facility would be equipped with a proton accelerator and two treatment gantries, with a view to treating 1,500 patients annually after a ramping-up phase.

Given the strong scientific traditions, multi-disciplinary collaborations and solid data registries in the country, the panel finds that Denmark has a special obligation to ensure that the center becomes a truly national center ensuring a strong collaboration with referring departments. While the clinical need for proton radiotherapy is bound to increase in the near future, the panel did however advise not to rush the establishment of the Danish national center of proton radiotherapy, as efforts to do so in other countries have backfired.

Based on currently available evidence, the panel estimates that proton radiotherapy may be relevant in roughly 10-15% of all radiotherapy indications.

With roughly 12,000 new radiotherapy cases per year this corresponds to a potential annual case load of 1,200-1,800, of which proton radiotherapy would be indicated on a routine basis for a case load of around 200.

The panel found that the choice of equipment should be driven in the first place by strategic considerations. The panel underscored the need to establish a single, truly national center for particle radiotherapy, and that such a center should be flexible and expandable. The panel found that the Aarhus group presented the best implementation plan to allow for adjustments as experience grows, with annual capacity for new patients in the first two gantries reduced at 333 for 2017, and 666 for 2018, to allow for clinical implementation.

The panel found that a national particle radiotherapy center would need to focus on clinical research in areas with a potential benefit, and found that the Aarhus bid best addressed these issues, as they worked from an algorithm to list sites which would be treated with protons and presented a realistic strategy of selecting candidate sites for protocols strongly based in their research tradition and their existing participation and leadership of several Danish multi-disciplinary cancer groups.

The panel found the Aarhus group presented a convincing proposition to lead a national center of particle radiotherapy, with a designated future leader of a multi-disciplinary group, and having demonstrated their leadership through national and international collaborations. The panel also found the Aarhus group proposed a proper governance structure to ensure collaboration and ownership amongst all referring and contributing departments.

After reviewing the proposals to host a Danish national center of particle radiotherapy, and considering the best available evidence in the field, the panel recommends:

- That a single, national center of particle radiotherapy be established at Aarhus University Hospital
- Not to start, or give the appearance of starting, an equipment selection process too early and to ensure collaboration between the host institution, relevant authorities and expert advisors in establishing the top-level specifications for the equipment
- To project realistic capacities for the center, taking into account ramping up of staff and facility, and based on expected treatment protocols and number of fractions to be delivered per year
- That a strategic business case be developed to prepare for a proper budgeting model and subsequent tender for constructing and procuring equipment for the national center
- That governance structures be established to ensure a continued strong national clinical and scientific collaboration in the field of particle radiotherapy

## Summary in Danish

Ved protonterapi anvendes ladede partikler til at lave høj-energi præcisionsstråling der kan nedbryde kræftceller. Partikelterapi er særligt egnet til behandling af kræftsygdomme i barnealderen, da behandlingen kan reducere bivirkninger som f.eks. sekundære kræftsvulster. Behovet for etablering af et nationalt center for partikel stråleterapi i Danmark understreges af den øgede efterspørgsel og de stigende udgifter ved behandling af patienter i udlandet, kombineret med patientrettigheder for hurtig og rettidig behandling.

På begæring af Ministeriet for Sundhed og Forebyggelse er der foretaget en faglig vurdering af placeringen af ét nationalt center i Danmark, i regi af Sundhedsstyrelsen og med rådgivning fra et internationalt panel af eksperter på området. To ansøgninger blev vurderet: I den ene ansøgning, som er indsendt af Rigshospitalet, Københavns Universitet og Region Hovedstaden, foreslås centeret placeret ved Rigshospitalet. I den anden ansøgning, som er indsendt at Aarhus Universitetshospital, Aarhus Universitet og Region Midtjylland, foreslås centeret placeret i tilslutning til det nye universitetshospitalsbyggeri ved Skejby.

I ansøgningen fra Rigshospitalet foreslås et kompakt protonterapianlæg. Der argumenteres for at protonteknologien har undergået en betydelig udvikling, og at tiden er moden til en kompakt løsning. En kompakt protonterapiløsning med ét rum ville blive placeret i en ny, lille bygning, der kan placeres som en udvidelse af den nuværende Radioterapiklinik på Rigshospitalet, med en målsætning om at kunne behandle 450 patienter årligt fra første år, og senere udvidelse til 900 årligt.

Forslaget om at etablere et nationalt center for partikelterapi i Aarhus omfatter anvendelsen af relevante kommercielt tilgængelige teknologier der kan matche den overordnede vision og strategi for centreret, der foreslås opført på en ledig byggegrund ved den onkologiske afdeling ved det nye Aarhus Universitetshospital. Partikelcenteret vil blive udstyret med en protonaccelerator og initialt to behandlingsrum, med den målsætning at behandle 1.500 patienter årligt efter en indkøringsfase.

I betragtning af de stærke videnskabelige traditioner, det veletablerede multidisciplinære samarbejde og de robuste dataregistre i landet, finder panelet at Danmark har en særlig forpligtelse til at sikre at centeret bliver et ægte nationalt center der sikrer et stærkt samarbejde med henvisende afdelinger. Selvom det kliniske behov for protonterapi vil stige i den nærmeste fremtid er det dog samtidig panelets anbefaling at man ikke skal forcere etableringen af det danske nationale center, da tilsvarende hastværk i andre lande har givet bagslag.

Baseret på tilgængelig viden har panelet vurderet at protonterapi kan være relevant i ca. 10-15 % af alle tilfælde hvor stråleterapi er indiceret. Med årligt ca. 12.000 nye strålepatienter i Danmark svarer dette til et potentielt år-

ligt patientvolumen på 1.200-1.800, hvoraf protonterapi vil være rutinemæssigt indiceret hos ca. 200.

Panelet fandt at valget af udstyr bør bestemmes primært ud fra strategiske overvejelser. Panelet understregede vigtigheden af at etablere ét enkelt, ægte nationalt center for protonbehandling, og at et sådant center bør være fleksibelt med mulighed for udbygning. Panelet fandt at forslaget fra Aarhus indeholdt den bedste plan for implementering, med plads til justeringer i takt med øget erfaring, og med målsætning om et årligt patientvolumen i de første to behandlingsrum reduceret til 333 i 2017 og 666 i 2018 for at muliggøre implementering i den daglige klinik.

Panelet fandt at et nationalt center for partikelterapi bør fokusere på klinisk forskning indenfor områder med potentiel gavn, og fandt at forslaget fra Aarhus bedst imødekom disse hensyn, ved at arbejde ud fra en algoritme ved valg af potentielle kræftformer til behandling med protoner, og ved at præsentere en realistisk strategi for udvælgelse af protokollerede behandlinger baseret på eksisterende samarbejde og lederskab indenfor en række danske multi-disciplinære cancergrupper.

Panelet fandt at de aarhusianske ansøgere præsenterede et overbevisende kandidatur til at lede det nationale center for partikelterapi, med en udpeget fremtidig leder forankret i et multi-disciplinært team, og med dokumenteret lederskab i nationale og internationale sammenslutninger. Panelet fandt også at ansøgningen fra Aarhus har foreslået en passende ramme for national styring af centeret, der sikrer samarbejde og ejerskab blandt alle henvisende og bidragende afdelinger.

Efter gennemgang af de to forslag til placering af et nationalt center for partikelterapi i Danmark, og under hensyntagen til den bedste tilgængelige viden på området, er det panelets anbefalinger:

- At der etableres et nationalt center for partikelterapi ved Aarhus Universitetshospital
- Ikke at påbegynde, eller give indtryk af at ville påbegynde, en proces med valg af udstyr for tidligt, og at sikre et samarbejde mellem værtsinstitution, relevante myndigheder og ekspertrådgivning ved kravspecifikation til udstyret
- At projektere realistiske kapaciteter for centeret, under hensyntagen til indkøring af personale og faciliteter, og baseret på forventninger om behandlingsprotokoller og antal fraktioner der skal leveres per år
- At en strategisk business case udvikles som forberedelse til en egentlig budgetmodel og efterfølgende udbud af anlægsopgaver og indkøb af udstyr til det nationale center
- At styringsrammerne for centeret fastlægges for at sikre et fortsat stærkt national klinisk og videnskabeligt samarbejde indenfor protonbehandling

## Context

Proton radiotherapy (PRT) uses charged particles to provide radiotherapy, thus delivering precision high-energy beams of particles to destroy cancer cells. PRT seems particularly suitable for childhood cancers, as there is a potential to reduce side-effects such as secondary cancers induced by radiotherapy when compared to conventional radiotherapy. In addition, the higher precision of PRT compared to conventional radiotherapy has proven value in the treatment of cancers growing in close proximity to sensitive healthy tissues such as brain, cranial nerves and spinal cord, which could otherwise not be treated with sufficiently high doses to achieve cure.

Current radiotherapy (RT) options have improved with the technological achievements of linear accelerators, and the integration with imaging technologies such as computer tomography (CT), magnetic resonance imaging (MRI) and combined positron emission and computer tomography (PET/CT). Image-guided radiotherapy (IGRT) has considerably reduced the uncertainties related to movement of the target between treatments, and is today considered the gold standard in RT. Intensity-modulated radiotherapy (IMRT) delivers dose distributions conformed to the target, and combined with IGRT have enabled treatment of tumor targets with relatively small margins, thus escalating doses and minimizing morbidity.

With PRT, a modality with improved depth-dose characteristics has been introduced. Protons differ fundamentally from photons delivered by conventional linear accelerators, in delivering low energy deposition of radiation while traversing healthy issue until reaching the target depth where the maximum energy (the Bragg peak) is deposited, with no appreciable tail. The depth is controlled by varying the energy of the charged protons, thus enabling a spread-out target area in all dimensions.

Protons are potentially advantageous to photons in ensuring that nearby normal tissues receive significantly less radiation, and thereby reducing adverse effects as well as delivering increased cure rate with higher radiation doses in certain cancers. PRT is estimated to reduce the dose to normal tissue by a factor of two. The strongest case for PRT is for the use in children with brain tumors, where the risk of secondary cancers caused by RT is of special concern, due to their long life expectancy following treatment in childhood and to their increased susceptibility to RT. From theoretical models it has been estimated that the life-time risk of secondary cancers after childhood RT for medulloblastoma may be reduced from 30% to 4% by PRT[1]. Further benefits from reduced radiation morbidity with PRT may include lower rates of deafness and of reduced IQ.

There is a dearth of good evidence to support the clinical benefit of PRT in most cancer types, and further evidence from basic, translational and clinical

[1] Mu X, Björk-Eriksson T, Nill S, et al. Does electron and proton therapy reduce the risk of radiation induced cancer after spinal irradiation for childhood medulloblastoma? A comparative treatment planning study. Acta Oncol 2005; 44: 554-62.

research is highly desired, as are health technology assessments including economic analyses. A Danish national center for PRT is expected to recruit a large proportion of patients into research protocols, thus also contributing high-quality science in the field.

PRT facilities use accelerators called cyclotrons, synchro-cyclotrons or synchrotrons to deliver proton beams for therapy, with most operational facilities using either cyclotrons or synchro-cyclotrons. Development and marketing of PRT accelerators is a dynamic and highly competitive field, with new accelerator concepts being explored, and several vendors active in the field. Traditional multi-room PRT facilities rely on a centralized accelerator with beam delivery to a number of treatment rooms equipped with gantries with rotational capabilities to increase flexibility in treatment planning. Newer, compact PRT systems integrate accelerator and treatment delivery systems (gantry and beam nozzle) in a single-room solution.

PRT facilities are unique in their size, complexity and cost of the technology. There are currently around forty operational PRT facilities around the world, with most of these in the USA and in Europe[2]. Additionally, more than twenty are in the planning stages and will become operational within the next five years. Both the Department of Health in England and the Ministry of Health, Welfare and Sports in the Netherlands have recently completed review processes to select suitable centers to host PRT facilities. In Scandinavia, PRT has been available for selected cases such as eye melanoma at the Svedberg Laboratory at the University of Uppsala, Sweden. In June 2011 construction was started of a dedicated PRT facility at the Akademiska Sjukhuset in Uppsala, expected to treat its first patient by 2015.

Capacities in the international PRT facilities are limited, and there are high costs involved in treating patients overseas, both in direct payments as well as by the burden imposed on children and their families having to spend extended periods of time abroad. Access to the European centers can be difficult, and costs for overseas treatment in the commercially run centers in the USA can easily exceed 1 million DKK. The increase in potential demand for PRT in the Danish population, as well as the rising costs and the requirements to treat malignant disease in a timely fashion, underscores the need to establish a national center for PRT in Denmark.

Currently, Danish patients can be referred, and fully reimbursed, for PRT abroad, subsequent to approval by the Danish Health and Medicines Authority (DHMA). In 2011, fifteen patients, mostly children, were treated abroad, and during the first nine months of 2012 twenty-two patients have been referred. As evidence and experience grows on the potential benefits from PRT compared to conventional radiotherapy, the need for PRT in the Danish population is expected to increase.

[2] http://ptcog.web.psi.ch/ptcentres.html

## Request for proposals

In July 2011, the Danish Ministry of Health issued a request for proposals (RFP) to host a national center for particle radiotherapy. The RFP was issued to two potential centers, who submitted their bids by end September 2011. In March 2012, the Ministry requested the DHMA to initiate a technical assessment on the establishment of one, single national Danish center.

Joint bids were received from two consortia: One proposal is to place the center adjacent to the Royal Hospital (Rigshospitalet) in Copenhagen; this application was submitted by the hospital, the University of Copenhagen and the Capital Region[3]. This will be referred to as the "Copenhagen bid"

The other application is for a national center for particle radiotherapy integrated into the new university hospital being constructed in Skejby outside of Aarhus; this application was submitted by the hospital, the University of Aarhus and the Region of Central Denmark[4]. This will be referred to as the "Aarhus bid".

In June 2012 a meeting was convened by the DHMA, with representatives from the two consortia, as well as the DHMA and the Danish Ministry of Health. The context and framework of the technical assessment was discussed, and the two consortia were invited to update and resubmit their applications, taking into account the time passed since the original request for proposals, technological and commercial developments in the field, changes in the consortias' staffing and research strategies, as well as radiation protection issues. A deadline of 3 September 2012 was agreed for the updated bid material.

## Convening an international panel of experts

To ensure the highest level of expertise, as well as balanced and impartial advice, it was decided to solicit the services of an international panel in the assessment of the two applications. With their bids both applicants submitted nominations for this international panel. Terms of reference for this advisory panel were developed (appendix A, see page 24) to describe the process of the technical assessment as well as the context and tasks of the international panel. The draft terms of reference and nominations for the panel was discussed at the June 2012 meeting and in subsequent bilateral consultations with the two consortia.

Early August 2012 the candidates had accepted and the panel was appointed by the DHMA, taking into consideration the nominations from the two applicants in a balanced approach.

The members of the international advisory panel were:

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[3] "Proposal for a Proton Therapy Center at Rigshospitalet", Volume I, Copenhagen, March 2011. "Research Strategy for a Proton Therapy Center at Rigshospitalet", Volume II, Copenhagen, May 2011. "Cancer Research at Rigshospitalet in 2009-2010", Volume III, Copenhagen, September 2012. "Update Proton Therapy Center at Rigshospitalet 2012", Copenhagen, August 2012.

[4] "The Danish National Center for Particle Radiotherapy", Aarhus, August 2012.

- Professor Michael Baumann, Dr.med.,
  Klinikdirektor, Klinik und Poliklinik für Strahlentherapie und Radioonkologie, Universitätsklinikum Carl Gustav Carus, Dresden
- Dr. Adrian Crellin,
  Consultant Clinical Oncologist, St James's University Hospital, Leeds, Chair of the NHS NSCT Proton Clinical Reference Panel and DH National Clinical Lead Proton Beam Therapy
- Professor Jürgen Debus, Dr.med., Dr.rer.nat.,
  Ärztlicher Direktor, Abteilung RadioOnkologie und Strahlentherapie, Nationales Centrum für Tumorerkrankungen, Universitätsklinikum, Heidelberg
- Professor emeritus Michael Goitein, PhD,
  Harvard Medical School, Boston, Massachusetts
- Professor Eric Klein, PhD,
  Chief of Physics, Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri

Memoranda of understanding were issued by the DHMA to the panel members, who in turn submitted statements on potential conflicts of interest as well as confidentiality statements, all of which are kept on file at the DHMA. Travel costs, lodging etc. for the panel members were covered by the DHMA, who also paid honoraria to the panel members for their services. Neither of the two bidding consortia nor any other outside parties, vendors etc. were involved in servicing the panel's work.

## Tasks of the panel and of the DHMA

The panel was asked to assist and advise the Danish Health and Medicines Authority on the following issues:

- to describe the role of a Danish national center for PRT, in the context of the present services offered Danish patients, and considering other international and regional developments in the delivery of PRT
- to outline a potential time frame for the establishment of a Danish national center for PRT, considering the expected technical and commercial developments in the field, as well as projections for the target population in need
- to balance and expand the criteria to be applied in assessing the two applicants
- to assess the two applicants according to the weighed criteria
- to provide, orally and in writing, contributions to the final report on the technical assessment

In reference to the legal context, the tasks of the Danish Health and Medicines Authority were:

- to select the members of the international advisory panel
- to convene, chair and keep the minutes of the international advisory panel
- to forward to the panel the two applicants' submissions, as well as other materials needed by the panel such as criteria and scoring tools

- to facilitate and prepare the assessment of the applications
- to compile contributions from the panel members
- to take authorship of the final report
- to acknowledge the contributions of the international advisory panel

## The deliberations of the panel

The updated bid documents, along with a brief guideline with suggestions for criteria to use in reviewing the bids, were sent to each of the panel members in early September 2012. The materials received by the five panel members were as listed in footnote 1-2 (see page 8) and appendices A-B (see pages 24 and 27).

On 9 October 2012 an all-day face-to face meeting of the panel was held in Copenhagen. Each consortium was invited to send representatives to meet the panel, and, at the request of the panel, it was suggested that they would represent the professional and clinical responsibilities of running the projected center. Each consortium met separately with the panel in equal time slots.

The Copenhagen bid was represented by:

- Professor Svend Aage Engelholm,
  Department of Radiotherapy
- Professor Liselotte Højgaard,
  Department of Clinical Physiology, Nuclear Medicine and PET
- Professor Søren Bentzen,
  Department of Radiotherapy
- Dr. Jannik Hilsted,
  Chief Medical Officer, Rigshospitalet

The Aarhus bid was represented by:

- Professor Jens Overgaard,
  Department of Experimental Clinical Oncology
- Professor Morten Høyer,
  Department of Oncology
- Professor Ludvig Muren,
  Departments of Oncology and Medical Physics
- Professor Cai Grau,
  Department of Oncology

From the DHMA, the meeting was chaired by Dr. Søren Brostrøm, Head of Division, and attended by Dr. Marie Brasholt, Senior Medical Officer; Stine Jønsson, Head of Section; Mette Øhlenschläger, Head of Division, National Institute of Radiation Protection, and Hanne Waltenburg, Deputy Head of Division, National Institute of Radiation Protection.

After the meeting, further input was solicited from the panel members, and draft versions of this report were compiled and circulated to the panel members for comments and revision. All members of the international panel of experts have agreed to the findings in this report.

### Legal context

The DHMA is empowered by the Health Act of 2008[5] to plan publicly funded specialized health services, including the detailed description of criteria and requirements, assessment of applications, and issuing (and revoking) permit to offer such specialized services. A consultative committee, chaired by the Managing Director of the DHMA, is heard in the process. As PRT easily fulfills the criteria for being a highly specialized service, these regulatory requirements apply, and the DHMA is empowered to decide the placement of a Danish national center for PRT.

The criteria currently used in assessing applications in this framework include, but are not limited to, the capacity and stability of a center's clinical services, its patient volume, clinical experience, and professional expertise, as well as its competency in all relevant professional and supportive fields. Further criteria are access to all required technical facilities, documented clinical quality and prospective reporting of results to relevant national databases, the employment of a multi-disciplinary approach as well as safeguards to ensure continuity of patient care. A center's active and documented research, development and education, its procedures for assessing new technologies and treatments and its collaboration with other hospitals and relevant specialized departments are also taken into account when assessing applications.

Additionally, the DHMA is the national radiation protection authority, regulating the use etc. of ionizing radiation. Based on international recommendations[6] and national legislation[7] the criteria currently used in assessing applications in the framework of radiation protection include, but are not limited to, the assessment of safety for the facility and activities, optimization of protection against radiation risks to patients, staff, members of the public and the environment to provide the highest level of safety that can reasonably be achieved as well as an assessment of a potential production of radioactive waste and radioactive releases over the lifetime of the facility.

These criteria also formed the basis for the panels assessment of the two applications to host a Danish national center for PRT (see page 18), and to aid the panel members in their review, a brief guideline on the applications of these criteria was provided by the DHMA (appendix B, see page 27).

## The two proposals

Joint bids were received from two consortia, referred to as the "Copenhagen bid" and the "Aarhus bid". Based on the bid materials received from the two consortia, the two bids are summarized here, quoting from the bids without judging their merits:

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[5] LBK nr 913 af 13/07/2010 (Sundhedsloven) §207-§209
[6] IAEA Safety Standards, No. GSR Part 4, "Safety Assessment for Facilities and Activities" (http://www-pub.iaea.org/MTCD/publications/PDF/Pub1375_web.pdf)
[7] BEK nr 823 af 31/10/1997 (Bekendtgørelse om dosisgrænser for ioniserende stråling)

## The Copenhagen bid

The Copenhagen consortium proposes to place a proton therapy center adjacent to the Royal Hospital (Rigshospitalet) in Copenhagen[8]. The original bid document was developed in the spring of 2011, and submitted by September of 2011. Subsequently, the bid material was updated with a volume IV, submitted in August 2012[9].

The Copenhagen bid envisages a proton radiation therapy center at Rigshospitalet interlinked with basic, translational and clinical research. The center should treat all Danish children with cancer, where radiation therapy is relevant (approximating 50 children annually). The proton therapy center should also treat adult cancer patients with cancer diseases, where proton therapy is recognized as the best treatment internationally, i.e. patients with melanoma in the eye, sarcomas in the skull base, cranio-pharyngeomas, selected gliomas, large arteriovenous malformations, meningeomas, pituitary tumor relapse, acusticus neurinomas, paranasal sinus carcinomas, nasopharyngeal carcinomas, paraspinal tumors, approximating a total of 300 patients annually.

For many other cancer types such as malignant melanoma, head and neck cancer, lung cancer, breast cancer, prostate cancer and cervical cancer the bid states that the role of proton therapy is not finally established, but proton therapy seems to be better than conventional treatment. The consortium therefore proposes a comprehensive prospective clinical trial program to gather evidence needed to establish the future role of proton therapy for a number of cancer diseases.

The overall aims of the Proton Therapy Center at Rigshospitalet are stated as:

1. To offer cancer patients the best possible radiation therapy, including proton therapy when proven or judged advantageous, striving for cure at the lowest possible cost in terms of side effects.
2. To develop a comprehensive medical physics research program on high-precision planning and delivery of proton therapy including motion management strategies, quantitation and visualization of uncertainties, adaptive strategies and use of bioeffect modeling for plan optimization and assessment of therapeutic ratio.
3. To pursue basic, translational and clinical research on the technical, biological and informatics basis for personalized proton therapy. This includes research into genetic and epigenetic biomarkers for tumor and normal tissue response to radiation.
4. To conduct research in molecular imaging, diagnostic imaging and image processing as a prerequisite for fully exploiting the capabili-

[8] "Proposal for a Proton Therapy Center at Rigshospitalet", Volume I, Copenhagen, March 2011. "Research Strategy for a Proton Therapy Center at Rigshospitalet", Volume II, Copenhagen, May 2011. "Cancer Research at Rigshospitalet in 2009-2010", Volume III, Copenhagen, September 2012.
[9] "Update Proton Therapy Center at Rigshospitalet 2012", Copenhagen, August 2012.

ties for spatial dose modulation with IMPT. This includes dose painting by numbers and theragnostic imaging, where specific areas of the tumor are treated to different dose levels.

5. To design, conduct and analyze the outcome of clinical trials with the aim of developing evidence based indications and test novel strategies for proton therapy in the multi-modality management of different cancer diseases.

As many of the operational particle therapy facilities in the world today are working without modern imaged guided technologies and possibilities for active modulation of the beam and even without gantries, the Copenhagen group aims for the Proton Therapy Center at Rigshospitalet to be among the absolute world leaders for proton therapy by this research based approach combining protons, imaging and molecular medicine.

In the 2011 bid materials the proposal is for a center with clinical patient treatment and research interlinked and integrated in one center, and situated in one building, with shared facilities including shared coffee rooms for clinical and research staff, and strong collaboration with the leading research groups at Rigshospitalet, and at the University of Copenhagen: The Faculty of Health Sciences, The Faculty of Life Sciences, The Faculty of Pharmaceutical Sciences and The Faculty of Science. Further strong collaborations would be with DTU, The Technical University of Denmark with the institutes IMM, Risø, Electro and BMC, and with strong collaboration with The Lund University Hospital, The University of Lund and especially the planned future ESS, The European Spallation Source with the data center in Copenhagen.

The research and clinical program would be anchored in an international setting with collaborative partners in Uppsala, Sweden and HIT Heidelberg, PSI, Villigen, Switzerland and first and foremost the University of Wisconsin, Madison, USA.

The bid suggests a solution for protons only, and not a solution for both protons and light ions. The expenditure to the much larger and more complex combined facility would not be justified, it is argued, and the few available clinical studies on the use of light ions do not show convincing results compared to results from the use of protons.

The bid states that the Department of Radiation Oncology at Rigshospitalet is the largest in Denmark and one of the largest in Northern Europe, and the department has pioneered the clinical implementation of a number of new radiation therapy technologies at the national and in several cases also the international level, including IMRT, gating and rotational delivery with RapidArc. The Department has a strong track record for dosimetric and quality assurance studies relating to the clinical introduction of new technologies. Parallel photon and proton therapy planning are already now conducted on selected cases in the Department with the aim of supporting decision making regarding referral to proton therapy abroad. Sharing knowledge and experience with a big radiotherapy clinic will give high synergy.

The Copenhagen bid outlines a vision for the center to deliver the most advanced patient treatment and the most excellent research in the triangle between science, technology and bio-medicine. In this vision, a cure of cancer without side effects is the final goal. It is stated that especially in children with cancer the center would have a beneficial treatment effect from the first treatments given, and that the center would be for the benefit of Danish patients, while the research outcome would be for the global benefit of the patients and society.

In the 2011 bid materials the future Proton Therapy Center at Rigshospitalet was projected to treat 1,000 patients per year and to be operational from 2015. The costs of establishing the center was listed as requiring a sum for equipment of 450 million DKK, a sum for building of 724 million DKK and a sum for the research center of 376 million DKK (excl. VAT).

However, in the updated Volume IV, completed in August 2012, the Copenhagen bid describes a proposal for a compact proton therapy facility solution. It is argued that proton delivery technologies have advanced considerably, and since the original bid was submitted the compact solutions have matured. Now, the time is ripe for a compact solution, the bid suggests.

A single room compact proton facility would be able to treat 450 patients per years and could be established in 3 years. The cost would be around 300 million DKK and the proton machine could be placed in a new small building as an extension to the existing Department of Radiotherapy at Rigshospitalet. It is argued that this technology would provide exactly the same patient treatment quality, including spot scanning, Intensity Modulated Proton Therapy (IMPT) and Image-Guided Radiation Therapy (IGRT), as the larger, traditional facilities. A second treatment room could be added in the future, should the clinical need be there, whereby the treatment capacity can be expanded to 900 patients per year.

The lower capital investment and the option for a phased expansion of capacity make the proposed clinical compact proton solution, in the view of the bidders, the optimal choice for Denmark with a population of 5.5 million people. From an evidence-based medicine perspective, the phased introduction of proton therapy in Denmark would minimize the risk of investing in a large, traditional facility with excess treatment capacity or with an implicit pressure to give proton therapy to patients in whom there is only weak or no evidence for a favorable cost-benefit compared to photon therapy.

The bid material assesses the technical specifications of the three commercially available compact solutions: Mevion S250™, Varian ProBeam™ and IBA ProteusOne™ and finds all three systems to meet the clinical needs and would provide adequate support for the research projects described in Volume II of the original application. International collaboration on clinical trials would ensure patient enrolment already with one treatment room available. The first phase of a compact proton facility would open for patient treatment much earlier than would be the case with a traditional proton facility, and with no foreseeable drawback for the planned research program.

The Copenhagen bid argues that they have detailed plans, the physical location and the economical basis in place for the one room compact facility, which could be extended to a two room facility, if or when the clinical need arises. The consortium underlines their motivation, their overall research strategy and their required clinical and research expertise to succeed.

### The Aarhus bid

The Aarhus consortium proposes a national center for particle radiotherapy integrated into the new university hospital being developed in Skejby outside of Aarhus[10]. The bid document describes the design, aims and operation of a particle radiotherapy center to be placed at the new University Hospital in Aarhus.

The bid states that the center would be integrated into a comprehensive interdisciplinary academic environment combining the clinical services of the top university hospital in Denmark, the largest radiation oncology research center in Scandinavia and the only center for accelerator physics in Denmark.

The long-term vision of the proposed National Center for Particle Radiotherapy (NCPRT) is stated as delivering frontline research-based proton therapy to all relevant Danish patients, and becoming a world leader in research and treatment of cancer with particle based radiotherapy.

The bid finds commercially available technical solutions which match the overall vision and strategy for NCPRT. The proposed proton radiotherapy complex is planned to be built on a 9,000 $m^2$ building plot next to the Department of Oncology at the new Aarhus University Hospital, and it is stated that the plot is ready for construction to start immediately. Furthermore, the bid proposes that the 7,800 $m^2$ facility, for which comprehensive plans exist, would be equipped with a proton accelerator and two treatment gantries, with a view to treating 1,000 patients annually. The bid states that there would be well-integrated facilities for patients and their relatives, as well as clinical staff and scientists. Research office facilities would be planned in the NCPRT building close to the clinical activities, and there would also be an experimental particle beam facility, as well as experimental laboratories at the neighboring Core Research Center.

Future expansion would be secured through the possibility of a third gantry room, allowing smooth expansion up to a capacity of 1,500 patients annually. Should further expansion be needed, ample space would be reserved surrounding the facility.

Aarhus University Hospital, the bid argues, would be an optimal host for a Danish national particle radiotherapy facility. The comprehensive cancer management at Aarhus University Hospital is highly regarded internationally. Clinicians and scientists from Aarhus University Hospital play leading

[10] "The Danish National Center for Particle Radiotherapy", Aarhus, August 2012.

roles in all relevant Danish Multidisciplinary Cancer Groups and in most international scientific societies relevant for radiation oncology. The Department of Oncology hosts an internationally renowned clinical and experimental environment with a very high academic production; more than half of all scientific papers from the six Danish oncology departments over the last decades have a first author from Aarhus University Hospital.

The consortium claims a broad international network, especially through participation in all radiation oncology relevant FP5, FP6 and FP7 EU research programs: Scientists from Aarhus University and Aarhus University Hospital have a long time standing special strength in accelerator physics and particle beam radiotherapy research, where they, as partners in international research collaborations, have been responsible for the radiobiology and dosimetry associated with major particle beam experiments, for example at CERN. The laboratories are equipped for radiobiological dosimetry measurements using refined particle beam structures. Additionally, Aarhus University Hospital and Aarhus University host several interdisciplinary centers, which would be actively involved in the research at NCPRT.

The bid argues that research activities in the center would exploit the synergistic effect of collaboration between existing leading major research groups in the fields of clinical radiobiology, functional imaging, accelerator physics, medical physics, cellular and molecular oncology, nanotechnology and clinical research in Aarhus. The lead scientists at NCPRT, it is claimed, have a strong track record in collaborating with the Danish radiotherapy community and the Danish Multidisciplinary Cancer Groups, and they have shown excellent leadership skills in the national radiotherapy research center CIRRO, which is initiated and hosted by Aarhus University and Aarhus University Hospital. In addition, a unique international network exists that is associated with particle therapy spanning most relevant major institutions and collaborative groups, both throughout Europe and world-wide.

A comprehensive research program is planned, the bid describes. Particle therapy is a new enterprise and while extremely promising, it requires more clinical data for assessment of its outcome. In this new therapy area, reliable clinical studies are presently few and far between and an important mission of the new center is to help overcoming this current lack of information. With this in view it is planned to include a very large proportion of the patients in clinical trials. The trials will in particular aim to establish the types of cancers which are most suitable for particle therapy. Clinical treatment protocols would be established on the basis of evidence from the clinical outcome after proton therapy and analyzed and discussed within the rapidly growing world forum for particle therapy. The basic and translational research, conducted in the radiobiology and functional imaging programs, would aim to characterize the individual normal tissue and tumor biology relevant for proton therapy. These activities would be further facilitated by establishing a particle radiotherapy dose-plan database and utilizing existing tissue and tumor bio-banks. Essentially the research in treatment delivery

and dose planning is closely allied to practice and will have as its major aim the improvement of the precision and quality of particle radiotherapy.

The planned research staff would include a director, 28 full time academic positions, 17 technical-administrative positions and 4 visiting scientist positions. Within the field of education related to the new center, the majority of all Danish pre- and postgraduate educational activities in radiotherapy and medical physics are located in Aarhus. Activities include national specialist courses for oncology residents, a school for radiotherapists, a dedicated medical physics module at Aarhus University and the Danish Graduate School in Clinical Oncology. These educational activities would be expanded to encompass particle radiotherapy, exploiting the local accelerator expertise in this area. In addition, core groups would be trained at international reference centers and Danish doctors in training would be offered courses at the NCPRT.

The NCPRT would be embedded with the Center for Cancer and Inflammation at Aarhus University Hospital and governance enabled according to the high standards associated within this institution. The day-to-day management team would consist of the three directors of Clinical Management, Technical Management and Research, respectively. The national governance of the NCPRT would be secured through a National Board, with representatives of key stakeholders, that is, the Ministry of Health, Danish Regions, Danish Multidisciplinary Cancer Groups and others. An International Advisory Board and a National Forum for Particle Radiotherapy would secure input from experts and collaborators in Denmark and abroad. Contact persons would be assigned at all Danish radiotherapy departments. In order to facilitate smooth patient throughput with the maximum of communication, regular meetings and video conferences, as well as the use of comparative treatment planning IT infrastructure, are planned between referring specialists and the center.

The construction costs are estimated in the bid material as 770 million DKK (building 295 million DDK, equipment 475 million DKK), a budget comparable to similar recent state-of-the-art facilities in Europe. The estimated annual operational costs at full operation of 1000 patients per year would be 76 million DKK. The average annual research budget would be 36 million DKK. Since construction is ready to start from today the center could open its doors to the first patients by the end of 2017 if a decision for its location is made in 2013.

The commitment of Aarhus University Hospital and Aarhus University to the project is underlined in the bid materials, with a commitment of the institutions together to have agreed to contribute initially with 50 million DKK to the project, in addition to the value of the building plot.

## The panel's assessment of the two proposals

Overall, the panel finds the establishment of a single national center of PRT in Denmark to be a very worthwhile endeavor. With a population of 5.6 million inhabitants served by a well-integrated and comprehensive health-care system, with indeed very strong scientific and clinical traditions in clinical oncology and radiotherapy, such a center could certainly be sustained.

Given the strong scientific traditions, multi-disciplinary collaborations and solid data registries in the country, the panel also finds that Denmark has a special obligation to ensure that the center becomes a truly national center with a strong collaboration with referring departments, to produce robust and original science in the field.

While the clinical need for PRT is bound to increase in the near future, the panel does however advise not to rush the establishment of the Danish national center of PRT, as efforts to do so in other countries have backfired.

### Estimates of the target population

Based on currently available evidence, the panel estimates that proton radiotherapy may be relevant in roughly 10-15% of all radiotherapy indications. With roughly 12,000 new cases per year with radiotherapy indications this corresponds to a potential annual case load of 1,200-1,800. The panel also found the algorithm proposed by the Health Council of the Netherlands[11] helpful, for grouping indications in three categories, based on expected advantage of protons over photons according to set criteria in the individual clinical situation, taking into account normal tissue complication probability models.

In the first category, where the expected advantage is major in favor of protons, the panel would group commonly accepted indications such as curative treatment in pediatric cases and a number of adult indications such as base of skull and spinal chordomas and chondrosarcomas, as well as selected head and neck cancers and other difficult cases. Based on best available evidence this population of PRT indicated on a routine basis would be roughly 15% of all PRT cases, or an annual case load of around 200. Similar population estimates have been done recently when planning for the national proton therapy service in England[12].

The panel found that the few Danish cases of intraocular melanoma, that are already today being referred abroad to specialized onco-ophtalmological centers, should continue to do so, as this small and highly specialized niche would be difficult to accommodate in a Danish center.

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[11] "Proton radiotherapy. Horizon Scanning Report". Gezondheidsraad, Den Haag 2009.

[12] "A Framework for the Development of Proton Beam Therapy Services in England". Department of Health, London, July 2009. "National Proton Beam Thearapy Service Development Programme. Strategic Outline Case". Department of Health, London, October 2012.

The second category, where the expected advantage of protons is moderate or questionable, the panel would estimate at roughly 85% or an annual case load of 1,300. These patients should be enrolled in clinical trials or protocols to establish evidence, and a primary aim of the Danish national center should be to ensure well-designed trials with adequate patient numbers. To the extent that comparative trials are conducted with conventional RT arms, the projected throughput of the PRT facility would obviously be lower.

The third category, where the expected advantage of protons is small or absent, should continue to be offered photon radiotherapy.

## Equipment and facilities

In general, the panel found that it would be wise not to start, or give the appearance of starting, an equipment selection process too early. The legal requirements for equipment procurement are very demanding and failure to follow the required procedures can badly delay a project and even derail it, as has been the case in several European countries.

The choice of equipment should be driven in the first place by strategic considerations. Both applicants seem to accept the proposition that the equipment should, to the extent possible, allow the protons to be used to their full potential. This has many aspects, but not least of these is the ability to perform intensity-modulated particle radiotherapy at the highest possible level.

The panel would not advise the selection of an applicant based in part on their preference for a given device but, rather, to defer the equipment selection process (and budget) until the host institution for the facility is selected. The host institution should then work with relevant authorities and outside experts to undertake a selection process – which must start with quite detailed specifications of what is desired and a balanced estimation of risk between both what it currently clinically available and what is promised by manufacturers.

The panel considers it a mistake to select an institution based in part on their preference for a lower cost option. Indeed, when the overall cost of starting the project up and running it for 10 to 20 years is tallied up, the initial cost of the equipment will fade as the running costs over a decade could sum up to significantly higher amounts than initial investments. Down the road it will be seen to have been a far better decision to have picked the best available technology, with capabilities of further development and upgrading as technology inevitably changes.

The panel underscored the need to establish a single, truly national center for PRT, and finds it important that such a center be flexible and expandable. In this regard the panel did not regard the proposal of the Copenhagen bid of adding single-room solutions one at a time, as if conceptually just expanding an existing string of photon accelerators, as particularly wise, as this facility could easily be constrained for options to accommodate future technological solutions.

Both applications have proposed very attractive designs for their facility. The size of the building is in part determined by the equipment and in part by the clinical and research activities which it houses. The vendor of the proton therapy equipment and the detailed nature of what is being bought must be decided before the building design can be finalized – and the panel found it wise not to go too far down the road of building design before that time.

The panel did commend both applicants for proposing integrated PRT facilities with existing radiotherapy departments in full-scale university hospitals, as stand-alone PRT facilities elsewhere have shown to have difficulties ensuring continuity of patient care.

In connection with the equipment, in formulating the business plan it is important to appreciate that substantial staffing is needed several years before start of operations. They are needed to: plan and develop specifications for the facility and especially its equipment; oversee the design and construction of the facility; prepare the infrastructure for treatments (instrumentation, computer programs etc.); conduct acceptance tests of the equipment; and commission it.

### Safety issues

The panel found that both proposals at this stage addressed relevant safety issues, such as shielding, safety of staff and individual monitoring. The panel found that both applicants acknowledge and oblige to meet the requirements set by DHMS as the regulatory authority during planning, operation and decommissioning of the PRT facility.

### Delivering clinical services

In assessing the two proposals, the panel found both bids to have access to necessary and relevant supportive services, including co-location of imaging, pediatric, oncological and anesthesiological services, as well as child and family friendly facilities and on-site guest houses.

However, the panel did find that realistic projection for patient throughput is needed. Operation of the currently available proton therapy equipment is, by and large, clumsy and inefficient, and does not approach the standards of conventional radiotherapy. While current proton users are resigned to this, newcomers to the field are often largely uninformed and do not pressure vendors to address this problem. Ramping up of staff and facilities will take time.

The panel found that the projected volume of 450 patients per year in a one-room solution starting in 2016, as proposed by the Copenhagen bid, was unrealistic, and failed to get adequate responses to queries on this central issue. Furthermore, the panel was not convinced that the Copenhagen bid had the staffing plans and training scenarios necessary to ramp up staffs in time for a 2016 throughput as proposed. Training, including spending time at existing high-quality proton centers for a minimum of one and preferably more years would be important before operation begins. An enormous amount of plan-

ning and preparation (in all disciplines) is needed well before operations begin – and, for these to be effective, considerable training/experience must already have been obtained

The panel found the Aarhus group presented a realistic implementation plan to allow for adjustments as experience grows. The Aarhus bid proposes to appoint the management group already in 2013 to prepare the procurement of the proton radiotherapy system and to manage the planning of the national center of PRT. Three physicists would start education, training and preparation in advance, to be an active part in the installment in 2016 and treating the first patients in 2017. The annual capacity for new patients in the first two gantries would be reduced at 333 for 2017 and 666 for 2018 to allow for clinical implementation. Decision on a third gantry would be made after three full years of operation.

For future planning and projections of the national center for PRT, the panel found that it would be advantageous to plan capacities for the center in the ramping up phase based on expected treatment protocols and number of fractions to be delivered per year. In both centers' cases there are assumptions on lower numbers of fractions used in modeled capacity than are delivered in patients treated in USA centers currently. The evidence base for hypo-fractionated regimes should be assessed before they are assumed and more detailed work on capacity modeling undertaken.

### Research strategies

There are particular issues with regards to the conduct of clinical research into proton beam therapy. These include: the choice of sites to investigate; stratagems to assure an adequate number of patients to conduct a given trial; and the provision of adequate resources for long-term follow-up of treated patients.

The panel found that the Aarhus group best addressed the issue of site selection, as they worked from the Dutch algorithm in listing sites which would be treated with protons and which would be considered in phase II or phase III trials. Furthermore, the panel found that the Aarhus group presented a realistic strategy of selecting candidate sites for protocols strongly based in their research tradition and their existing participation and leadership of several Danish multi-disciplinary cancer groups.

While there is no doubt that the NCPRT will be able to provide world-class clinical care for Danish patients, it is likely that, for some sites of interest, it may be hard to provide an adequate number of Danish patients for a clinical trial – especially in the case of phase III trials for which the control arm is likely to dilute the number of patients receiving proton therapy. Strategies to address this problem will be needed and are likely to include international multi-center trials and case-controlled studies with control arm patients being treated at non-proton centers. The NCPRT has the exciting possibility of taking a leading role in these efforts, but their pursuit will require substantial scientific dedication.

It is likely that an important benefit of proton therapy will be a reduction of late side-effects. These may occur even decades after treatment and may be quite subtle and of a nature as to be easily overlooked (e.g. complications of subsequent surgery in or near the proton-irradiated fields). Strategies and substantial resources will be needed to ensure continuity of patient referral, care, and follow-up – and even more so in the context of multi-center trials.

While both groups identified a number of potential research areas, the panel found that the majority of such projects proposed by both applicants do not relate specifically to proton or particle therapy per se. Rather, they have to do with radiation therapy in general, or even related fields such as imaging and tumor biology. That is not to say that developments in many of these areas would not profit patients who receive particle therapy. But it is unclear whether putting them all under the same roof as particle therapy: would be wise for programmatic reasons; would be of help when judging progress; or would make sense from a funding agency's point of view.

So far as the impact on proton therapy research is concerned, the panel sees two dangers. First, non-proton related research may dilute management attention on, and support of, efforts that are specifically proton-related. And second, in a somewhat related manner, it can have the undesirable consequence that, if progress on the proton therapy front were to be slow or problematic, it may be less quickly noted, or may be excused by good progress in these other areas. For that reason, proton therapy needs and deserves the full attention of a research group. General developments in radiation therapy are highly desirable, but they are a separate and potentially distracting problem.

Strong biology and technology laboratory research as well as strong translational research efforts are undoubtedly necessary to establish high quality proton therapy in a variety of indications and to assess its value compared to best conventional radiotherapy. However, this research needs to address specific issues which are very relevant for proton treatment and currently unsolved, such as motion management, relative biological effectiveness at beam edges, volume effects in healthy tissues, image guided intensity-modulated proton therapy approaches and, very importantly, patient stratification to the different treatment options.

### Leadership, governance and national collaboration

The panel found both applicants to have excellent scientists and staff in all the key disciplines at their disposal. It is also clear that the successful applicant will need to boost staffing, preferably including persons with experience in proton therapy.

However, the panel found that the Copenhagen application failed to clearly identify the person and core leadership group which would be designated to lead the proposed center, and failed to adequately respond when queried. The current department head will be of retirement age by the time the facility opens. Much of the research proposed in the bid is carried by experts in physiology, nuclear medicine and molecular imaging, and the group current-

ly does not seem to include an academic medical physicist although medical physics will have to play a major role in the project.

The panel found the Aarhus group to present a much more convincing proposition to lead a national center of PRT, with a designated future leader in his early fifties, and a strong core group in place covering radiotherapy, medical physics and clinical oncology. Furthermore, the Aarhus group has demonstrated their leadership skills through key roles in the Danish multidisciplinary cancer groups, and other national and international oncological and radiotherapy groups and societies, and they have since 2009 as leaders of the Lundbeck Foundation Center for Interventional Research in Radiation Oncology (CIRRO) proven their ability to host a national center.

Furthermore, the panel found that the Aarhus group proposes a sensible and realistic governance structure to ensure collaboration and ownership amongst all referring and contributing departments, including strategies to ensure continuity of patient referral and care, with a framework to ensure follow-up of patients over extremely long time periods.

## Recommendations

After reviewing the proposals to host a Danish national center of PRT, and considering the best available evidence in the field, the panel recommends:

- That a single, national center of particle radiotherapy be established at Aarhus University Hospital
- Not to start, or give the appearance of starting, an equipment selection process too early and to ensure collaboration between the host institution, relevant authorities and expert advisors in establishing the top-level specifications for the equipment
- To project realistic capacities for the center, taking into account ramping up of staff and facility, and based on expected treatment protocols and number of fractions to be delivered per year
- That a strategic business case be developed to prepare for a proper budgeting model and subsequent tender for constructing and procuring equipment for the national center
- That governance structures be put in place to ensure a continued strong national clinical and scientific collaboration in the field of particle radiotherapy

# Appendix A – Terms of reference

**Terms of reference for an international panel convened to advise the Danish Health and Medicines Authority on the establishment of a national center for particle radiotherapy**

In July 2011, the Danish Ministry of Health issued a request for proposals to host a national center for particle radiotherapy (PRT). The RFP was issued to two potential centers, who submitted their bids by end September 2011. In March 2012, the Ministry requested the Danish Health and Medicines Authority to initiate a technical assessment on the establishment of one, single national Danish center.

Furthermore, it has been agreed by all parties, that this technical assessment would optimally be served by an international advisory panel. These terms of reference describe the process of the technical assessment as well as the context and tasks of the international panel.

**Introduction**
Particle Radiotherapy (PRT) uses charged particles instead of X-rays to pro-vide radiotherapy, thus delivering precision high-energy beams of particles to destroy cancer cells. PRT seems particularly suitable for childhood cancers, as there is a potential to reduce side-effects and secondary cancers induced by radiotherapy when compared to conventional radiotherapy. How-ever there is currently a dearth of good evidence to support the clinical benefit of PRT in most cancer types, and further evidence from basic, translation-al and clinical research is highly desired, as are health economy analyses.

As it is difficult to estimate how many patients will potentially benefit from PRT as compared to conventional radiotherapy, it is not easy to plan for the present and future needs for PRT in the Danish population. Currently, Danish patient can be referred, and fully reimbursed, for PRT abroad, subsequent to approval by the Danish Health and Medicines Authority.

A Danish national center for PRT is expected to recruit a large number of patients into research protocols, thus also contributing high-quality science in the field.

**Context**
The Danish Health and Medicines Authority is empowered by the Health Act of 2008 to plan publicly funded specialized health services, including the detailed description of criteria and requirements, assessment of applications, and issuing (and revoking) permits to offer such specialized services. A consultative committee, chaired by the Director of the Danish Health and Medicines Authority, is heard in the process. As PRT easily fills the criteria for being a highly specialized service, these regulatory requirements apply, and the Danish Health and Medicines Authority is empowered to decide the placement of a Danish national center for PRT.

The criteria currently used in assessing applications in this framework include, but are not limited to:

- Capacity and stability of a center's clinical services
- Patient volume, clinical experience and professional expertise
- Competency in all relevant professional and supportive fields
- Access to all required technical facilities
- Documented clinical quality and prospective reporting of results to relevant national databases
- A multi-disciplinary approach
- Safeguards to ensure continuity of patient care
- Active and documented research, development and education
- Procedures for assessing new technologies and treatments
- Collaboration with other hospitals and relevant specialized departments

Additionally, the Danish Health and Medicines Authority is the national radiation protection authority, regulating the use etc. of ionizing radiation. Based on international recommendations and the national legislation the criteria currently used in assessing applications in the framework of radiation protection include, but are not limited to:

- Assessment of safety for the facility and activities
- Optimization of protection against radiation risks to patients, staff, members of the public and the environment to provide the highest level of safety that can reasonably be achieved
- Assessment of a potential production of radioactive waste and radio-active releases over the lifetime of the facility
-

These criteria will also form the basis for the assessment of the two applications to host a Danish national center for PRT. Applications have been received from two consortia: One suggests integrating it in the new university hospital being constructed in Skejby outside of Aarhus; this application is submitted by the hospital, the University of Aarhus and the Region of Central Denmark. The other application is to place the center adjacent to the Royal Hospital in Copenhagen; this application is submitted by the hospital, the University of Copenhagen and the Capital Region.
To ensure the highest level of expertise, as well as balanced and impartial advice, it has been decided to solicit the services of an international panel in the assessment of the two applications. Both applicants have, with their applications, submitted nominations for this international panel.

**Composition of the international advisory panel**
The panel will be composed of 5 internationally peer-recognized experts:

- 3 expert(s) from the field of oncological radiotherapy, and with specific experience and expertise in PRT
- 2 expert(s) from the field of medical physics, and with specific experience and expertise in PRT

The panel will be appointed by the Danish Health and Medicines Authority, taking into consideration the nominations from the two applicants in a balanced approach.

The Danish Health and Medicines Authority will cover travel, accommodation, per diem expenses, as well as honoraria, for the panel members. Memoranda of understanding will be issued to panel members, who will in turn be required to submit statements on potential conflicts of interest as well as confidentiality statements.

**Tasks of the international advisory panel**
The panel will be required to assist and advise the Danish Health and Medicines Authority on the following issues:

- to describe the role of a Danish national center for PRT, in the context of the present services offered Danish patients, and considering other international and regional developments in the delivery of PRT
- to outline a potential time frame for the establishment of a Danish national center for PRT, considering the expected technical and commercial developments in the field, as well as projections for the target population in need
- to balance and expand the criteria to be applied in assessing the two applicants
- to assess the two applicants according to the weighed criteria
- to provide, orally and in writing, contributions to the final report on the technical assessment

**The tasks of the Danish Health and Medicines Authority**
In reference to regulatory requirements, the Authority will:

- select the members of the international advisory panel
- convene, chair and keep the minutes of the international advisory panel
- forward to the panel the two applicants' submissions, as well as other materials needed by the panel such as criteria and scoring tools
- facilitate and prepare the assessment of the applications

- compile contributions from the panel members
- take authorship of the final report
- acknowledge the contributions of the international advisory panel

The result of this process will be a report, submitted to the Danish Ministry of Health, describing the establishment of a national center for PRT, as well as assessing the merits of the two applicants to see which should receive the first Danish national center for PRT.

**Time schedule (2012-2013)**

| | |
|---|---|
| End of April | Draft of terms of reference |
| May | Meeting to discuss process, with representatives of applicants, Ministry of Health, and the Danish Health and Medicines Authority |
| End of June | Invitations sent to panel members, dates booked |
| Early September | Deadline, submission of supplementary material from the applicants to the Danish Health and Medicines Authority |
| September | Material sent to panel members |
| October | Face-to face meeting of the panel in Copenhagen. Representatives of the two applicants invited to attend brief hearings, if the panel so desires |
| November/January | Compilation of panel contributions. Possible follow-up video conference(s) with panel to discuss findings and recommendations |
| February | Final report submitted to the Ministry of Health |

# Appendix B – Criteria

**Brief guideline on the required evaluation regarding the establishment of a Danish center for particle radiotherapy**

Rigshospitalet and Aarhus University Hospital are among the largest tertiary university hospitals in Denmark. Both hospitals have direct access to a large number of highly specialized functions and co-location of imaging, pediatric and oncology services as well as patient hotels. Both hospitals are situated in or near the city with easy access.

The international advisory panel should:

- describe the role of a Danish national center for PRT, in the context of the present services offered Danish patients, and considering other international and regional developments in the delivery of PRT
- outline a potential time frame for the establishment of a Danish national center for PRT, considering the expected technical and commercial developments in the field, as well as projections for the target population in need
- balance and expand the criteria to be applied in assessing the two applicants
- assess the two applicants according to the weighed criteria
- provide, orally and in writing, contributions to the final report on the technical assessment

The national planning of specialized health care services in Denmark is regulated by the Health Care Act and a task of the National Health and Medicines Authority. The criteria previously used by the Authority when judging applications should, if possible, be broadly applied when assessing the two applications for the national center of particle therapy. –The Authority would ask the panel members to consider these criteria when reviewing the two applications and proposing their recommendations to the Authority. The panel can expand on the criteria, if necessary.

These criteria can be summarized as follows:

- Capacity and stability of a center's clinical services, including
    - Realistic timelines for development and implementation of services
    - Sufficient capacity to cover projected treatment needs
    - A clearly defined management with resources to manage the programme
    - A sufficient number of specialized and auxiliary staff to provide the clinical services at all relevant times
    - Plans to sustain and further develop the clinical services once the center is established
- Patient volume, clinical experience and professional expertise
    - A sufficient patient flow and volume to ensure maintenance of skills and ongoing development of clinical services
    - A sufficient number of specialized staff to sustain a professional environment that will ensure continuous development of services
- Competency in all relevant professional and supportive fields
    - Co-location of imaging, pediatric, and oncology services

    - Stable and direct access to other relevant clinical services necessary to a high complexity of clinical cases
- Access to all required technical facilities, e.g.:
    - Co-location and integration with existing radiotherapy infrastructure
- Documented clinical quality with prospective reporting of results to relevant national databases
    - Plans for the elaboration of relevant national clinical guidelines, patient pathways, referral criteria etc.
- A multi-disciplinary approach
    - Integration of professions, medical specialties, technical staff etc. in patient care
    - Plans to ensure that decisions are based on expertise from all relevant fields
- Safeguards to ensure continuity of patient care, e.g.
    - Plans to ensure seamless care for patients and professional communication with caregivers and treatment providers outside the center
    - Availability of accommodation for patients and their carers
- Active and documented research, development and education, e.g.:
    - Robust research links and infrastructure (multidisciplinary and international)
    - A relevant and ambitious strategy and roadmap for future clinical, physics and technological research and development
    - Plans to ensure sufficient training of staff during the implementation phase
    - A strategy to maintain skills and capability
- Technological capability, e.g.:
    - A site which meets technical and utility service requirements
    - An accelerator meeting the needs of capacity, indications and safety
    - Projections for technical development and upgradability
    - Procedures for assessing new technologies and treatments
- Collaboration with other hospitals and relevant specialized departments, including
    - Relevant plans for ensuring efficient and professional communication with caregivers and treatment providers outside the center

Criteria regarding the framework of radiation protection - which are also to be used in assessing the applications - are based on international recommendations (IAEA Safety Standards[13]) and the national legislation and include, but are not limited to:

- Assessment of safety for the facility and activities
- Optimization of protection against radiation risks to patients, staff, members of the public and the environment to provide the highest level of safety that can reasonably be achieved
- Assessment of a potential production of radioactive waste and radio-active releases over the lifetime of the facility

The relative weighing of the criteria will be discussed during the meeting of the advisory panel.

[13] IAEA Safety Standards, No. GSR Part 4, "Safety Assessment for Facilities and Activities" (http://www-pub.iaea.org/MTCD/publications/PDF/Pub1375_web.pdf)

# Appendix C – Abbreviations

| | |
|---|---|
| **CT** | computer tomography |
| **DHMA** | Danish Health and Medicines Authority |
| **IGRT** | image-guided radiotherapy |
| **IMRT** | intensity-modulated radiotherapy |
| **MRI** | magnetic resonance imaging |
| **NCPRT** | National Center for Particle Radiotherapy |
| **PET/CT** | combined positron emission and computer tomography |
| **PRT** | proton radiotherapy |
| **RFP** | request for proposals |
| **RT** | radiation therapy |