CERN Baltic Group

Report on workshop

Particle therapy – future for the Baltic States? State-of-play, synergies and challenges

Introduction and overview

At 9th General Meeting of the CERN Baltic Group (CBG)[1] a designated Working Group "Advanced Particle Therapy Center in the Baltic States" (APTC) has been established, with professor Toms Torims (Riga Technical University) as the Convener of the Working Group and professor Diana Adliene (Kaunas University of Technology) as Deputy Convener. Mandate of the Working Group is the development of a flagship project within the CBG framework - creation of a modern, innovative research and cancer treatment center in the Baltic States in a close partnership with CERN Next Ion Medical Machine Study (NIMMS)[2] collaboration experts.

In spring of 2022, a dedicated concept paper has been developed for the proposed initiative. It was presented at different levels to various scientific, political and medical community stakeholders. Furthermore, at the end of 2022 in all three Baltic States, representatives of medical communities, research institutions and relevant ministries were invited to bi-lateral meetings with the Working Group representatives:

- October 18th – Riga, Latvia[3];
- November 16th – Kaunas, Lithuania[4];
- November 22nd – Tallinn, Estonia[5].

The main goals of these meetings were to inform the communities on the overall technical concept of the facility and status of the initiative, as well as to discuss the view of the community on the project idea. Through these discussions, key critical aspects were identified for further work for future developments of the initiative: cancer statistics in the Baltic States region, clinical indications for proton therapy, technology readiness level of the proposed technology and accelerator complex, possible synergies with the nuclear medicine field and educational pathways necessary for personnel at such a facility.

In order to build on the mentioned discussions and to comprehensively adress the identified critical aspects of the "*Advanced Particle Therapy Center in the Baltic States*" initiative among the key experts of the Baltic States in the involved fields, a workshop "*Particle therapy – future for the Baltic States? State-of-play, synergies and challenges*" was held at the European Organization for Nuclear Research (CERN) on 25th of May, 2023. In the workshop Baltic States was represented both in-person and remotely by experts in clinical radiation therapy, nuclear medicine, radiology and medical physics, with political stakeholders engagement from side of Baltic Assembly representatives. Technological aspects were covered with participation of NIMMS collaboration experts.

This report outlines the key findings and outcomes of the workshop, which are indispensable for the next steps and developments in the future of the project initiative.

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[1] https://indico.cern.ch/event/1138329/
[2] https://kt.cern/kt-fund/projects/nimms-next-ion-medical-machine-study
[3] https://indico.cern.ch/category/16259/attachments/2587678/4464652/Summary_LVA_18_10_2022.pdf
[4] https://indico.cern.ch/category/16259/attachments/2587678/4464651/Summary_LTU_16_11_2022.pdf
[5] https://indico.cern.ch/category/16259/attachments/2587678/4464650/Summary_EST_22_11_22.pdf

Goals of the workshop

1. To **bring together high level professionals, experts and stakeholders from the Baltic States, nominated by the corresponding professional associations** in the fields of clinical radiation therapy, nuclear medicine, radiology, medical physics and others involved to discuss and work on ideas for development of key aspects of the "*Advanced Particle Therapy Center in the Baltic States*" initiative.
2. To **provide fact-based and scientifically driven reasoning for each of the key aspects** of the "*Advanced Particle Therapy Center in the Baltic States*" initiative based on the afore mentioned stakeholder opinion.
3. To **build multi-disciplinary synergies** between the different fields and specialities involved in cancer treatment and three Baltic States at large.
4. To **introduce** professionals and experts from the Baltic States with **scientific activities at CERN for medical applications and technology transfer to the clinic**.
5. To **reach a joint consensus and vision of future development** of the "*Advanced Particle Therapy Center in the Baltic States*" initiative based on the conclusions reached within the workshop.

Structure of the report

Report is structured according to the different sessions held within the workshop, indicating key considerations and findings as discussed in each of them:

- *Cancer statistics and indication profile in the Baltic States. Status of radiotherapy technologies in the Baltic States* – indicating the first statistical results found in a recent study in the Baltic States on cancer incidence, mortality and radiotherapy capacity, as well focusing on the translation of these results to applicability of particle therapy.
- *Clinical indications for proton and particle therapy. Existing clinical evidence and on-going clinical trials* – indicating the clinical evidence and general spectrum of clinical indications applicable for particle therapy, while shortly indicating approaches for patient selection as alternatives to evidence based medicine.
- *The technology of helium synchrotron: technology readiness level and research needed* – the technological development level of the particle accelerator technology proposed for the facility is presented, indicating the different involved technologies and components, as well as general development time-frame.
- *Current status of nuclear medicine in the Baltic States. Trends and research pathways going into the future* – findings on development trends of nuclear medicine field in Europe, as well as current status and future plans in the Baltic States region are presented. A technological synergy perspective is also given for radioisotope production integration within the proposed facility.
- *Educational necessities and possible solution pathways for clinical and technical personnel training* – findings on conventional radiotherapy personnel statistics in the Baltics and professional viewpoints on necessary "particle therapy oriented" training are given. Various personnel and expert training approaches are presented from perspective of previous European projects.

At the end of the report, overall conclusions and future steps of the project initiative are given. For detailed reports presented on each of the sessions and respective references, the dedicated workshop *Indico* page is to be consulted[6].

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[6] https://indico.cern.ch/event/1251461/timetable/

Cancer statistics and indication profile in the Baltic States. Status of radiotherapy technologies in the Baltic States.

Speakers: Dr. **Manjit Dosanjh** (*University of Oxford, CERN*)
Dr. **Erika Korobeinikova** (*Lithuanian Society for Radiation Therapy, Lithuanian University of Health Sciences*)
Mr. **Kristaps Palskis** (*Riga Technical University, CERN*)
Moderator: Dr. **Dace Bogorada-Saukuma** (*Latvian Therapeutic Radiology Association*)

As an introduction, outlook by considering the global perspective of cancer incidence and mortality was given. **In the year of 2020, 19.3 million new cases were diagnosed with 9.96 million deaths** [1]**.** General trends of cancer developments indicate a steady increase, with projections **showing 27.5 million new cases per year and 16.3 million deaths by year 2040** [2][3]. In the treatment of oncological malignancies, radiation therapy stands as one of the modalities, which, according to global consensus and guidelines, would be necessary for treatment of about 50 % of cancer cases [4] [5]. With the main aim of radiation therapy to deliver the treatment dose of ionizing radiation to the tumor volume, while maximally sparing the surrounding normal tissue and critical organs, different modalities can be used – X-ray photons, electrons, as well as heavier particles – protons and ions. Thus, a crucial point – **by no means the clinical essence of particle therapy is different than conventional radiation therapy**. Therefore, particle therapy is another modality in the wide array of radiotherapy techniques. Throughout the years, particle therapy has undergone major developments and currently there are around **130 particle therapy centers around the world** with **280 000 patients treated with protons** and **40 000 – carbons ions** (*data of 2016*) [6].

From the European perspective, in 2002 the European Network for Light Ion Hadron Therapy (ENLIGHT) was established in order to coordinate the joint efforts and developments in particle therapy. Already then, one of the key areas of interest was the establishment of eligible patient numbers, as well – the clinical indications for particle therapy (*given in the next chapter of the report*). In the early 2000's from findings and estimates of the studies in Austria, France, Germany and Italy, following consensus points were reached within ENLIGHT network [7]:

- for every 10 million inhabitants around 20'000 patients yearly would receive conventional radiation therapy treatment;
- **12 % of these patients would largely benefit and be eligible for proton therapy –** thus around 2400 patients yearly per 10 million inhabitants;
- carbon ion therapy – more beneficial for radio-resistant tumors, accounting for around 600 patients yearly per 10 million inhabitants.

Looking at the geographical distribution of particle therapy centers within Europe, there is **a lack of facilities in the eastern part of Europe, encompassing the Baltic States, Finland, Belarus, Ukraine and South-East European countries**. To address this, similarly to the "*Advanced Particle Therapy center for the Baltic States*" initiative there already exists an established initiative for particle therapy center development in the South-East European countries – SEEIIST. Looking at the SEEIIST initiative and it's early stages of development, data that were collected for assessment of radiotherapy technological and human capacity in South-East Europe region in the perspective of particle therapy developments [8] [9]:

- cancer incidence and mortality data;
- data on technological equipment required for radiotherapy – both diagnostic imaging and treatment units;
- cancer incidence and mortality data stratification based on cancer type, assessing numbers in particular localization more-readily eligible for particle therapy.

By analogy, similar data collection routine would be of interest in the Baltic States for assessment in the perspective of this initiative.

Large part of this necessary data was collected in 2022 as the Baltic States were one of the participants in the *Access to Radiotherapy Technology (ART) study* [10]. The data collected in this study gave clear key metrics indicating the current status and level of conventional radiotherapy in the Baltic States region. The key metrics as total over the 3 countries were reported as follows [11]:

- in terms of diagnostic imaging, 169 computed tomography (CT), 111 mammography, 94 magnetic resonance imaging (MRI), 13 single-photon emission computed tomography (SPECT) and 9 positron emission tomography (PET) units are present. **Such a number of diagnostic imaging units can be deemed sufficient for cancer diagnostics in accordance to international guidelines** [12].
- in terms of treatment units, 26 linear accelerator (LINAC) based external beam radiation therapy units are present, as well as 7 brachytherapy units. All of the treatment units are state-of-art, capable of delivering advanced radiotherapy techniques, as well as dedicated systems such as *CyberKnife, GammaKnife* and on-going installation of therapy unit with integrated magnetic resonance imaging are present in the region. **The number of available radiotherapy treatment units is thus in accordance with suggestions from International Atomic Energy Agency (IAEA) and other relevant guidelines** [13] [14]**.**
- according to the **data of 2021** (*or 2020, depending on the country*), around **38000 new cancer cases** were registered**,** while around **17900 cancer deaths** were registered. With the **total population in the Baltic States of 6.02 million**, the crude, non age-specific corrected **cancer incidence and mortality rates are 632 and 297 per 100 000 inhabitants**, respectively.
- out of the registered cancer cases, in 2020 a **total of about 13045 patients received conventional radiotherapy** as cancer treatment procedure. This number corresponds to **around 34 % of all registered cancer cases**, which generally is lower than the international consensus of about 50 % of cancer patients that should receive radiotherapy as part of cancer treatment course. The root cause for this should be investigated further.
- overall, the gathered data show **"well-shaped" technical resources in conventional radiotherapy**, but the "mortality/incidence" index should be improved to reach the level of higher income countries.

By analogy of SEEIIST initiative activities, the stratified data of cancer incidence by type are necessary to indicate cancer statistics of localizations benefitting most from particle therapy. Another survey was prepared and preliminary data for the Baltic States have been collected in early 2023, indicating incidence and other parameters for cancer types that are most commonly considered as eligible for particle therapy. The key findings reported were as follows [11]:

- most common cancer types that are newly registered are similar between the Baltic States (*see note at the end of this chapter*) – prostate, non-melanoma skin cancer, lung, breast, colon, stomach, rectum, kidney, gynecological and pancreatic cancers, respectively.
- cancer types associated with largest mortality are likewise similar between the Baltic States – lung, colorectal, stomach and liver cancers, respectively. Thus**, cancer**

types with both the highest incidence and mortality in the Baltic States generally follow the global trends [15]**.**

- pediatric cancers are one of the most common indications for particle, specifically – proton therapy. Key metrics collected for pediatric cancers:
    - over the period of last 5 years, around **1020 new pediatric cancer cases have been registered in the 3 Baltic States in total**;
    - out of all the registered cases, around **210 pediatric patients have received radiation therapy treatment** in the last 5 years, around **40 patients in last reported year**;
    - most common pediatric cancer types: leukemia, brain and central nervous system tumors, bone, connective and soft tissue cancers, lymphoma.
- as the other key indications eligible for particle therapy, data on incidence (*patients receiving radiotherapy in case of data corresponding to Latvia*) were collected for brain tumors and glioblastoma specifically, head and neck tumors and pancreatic cancer. Importantly, pancreatic cancer is commonly not treated with radiation therapy within the Baltic States.

As last question in the newly prepared survey was **projections of patients benefitting from particle therapy in the Baltic States based on the current knowledge of the experts in the region**. Interestingly, no common answer could be reached between the experts from the region, thus clearly indicating also in discussions of workshop participants – **larger knowledge base and particle therapy education is needed in Baltic States region in order to reach a joint consensus.** To give first estimates of the number of patients eligible to proton and particle therapy in the region, various studies and consensus statements had been researched prior and discussed within the workshop [11]:

- data of United States, 2018 – **2.2 % of all radiotherapy receiving patients** were considered eligible and received proton therapy [16];
- data of United Kingdom, 2018 – **1.5 % of all radiotherapy receiving patients** were considered eligible and received proton therapy [17];
- a 2005 study of Swedish radiation oncologist and medical physicist group – **14 – 15 % of all radiotherapy receiving patients** would have increased enough therapeutic benefit to justify use of proton therapy for treatment [18];
- a 2022 study in United Kingdom – **4.3 % of all radiotherapy receiving patients** would have increased therapeutic benefit either due to reduced toxicity or dose escalation possibility, justifying the use of proton therapy compared to conventional X-ray therapy [19];
- a 2021 study in Korea – an average of **10 % of all radiotherapy receiving patients** received proton therapy, based on data of 2 proton therapy centers [20].
- looking at the overall European proton therapy center statistics – **on average 223 adult and 150 pediatric patients receive this treatment modality yearly** (*data of 2020*) **per center** [21]**.**

Based on the researched consensus statements from proton therapy practicing groups and radiotherapy statistics, **first estimates would suggest around 560 to 1950 patients yearly eligible for proton therapy from all 3 Baltic States**, corresponding to the estimate levels of 4.3 % and 15 %, respectively, as reported. As general particle therapy practice has shown that **around 200 to 500 patients per treatment room annually** to be a sufficient metric, the first, crude estimates indicate possibly sufficient number of eligible patients.

Though it was agreed in the discussions of the workshop that further in-depth analysis would be required, taking estimates based on particular cancer type incidence, as well as raising the general knowledge in particle therapy in the Baltic States would be necessary.

Apart from the eligibility statistics, other limiting problem factors were discussed. For example, from the perspective of data collected in Lithuania, only 1 patient has been referred for proton therapy to a clinic abroad, showing the complicated reimbursement system for such a radiotherapy modality, indicating the **need to address the particle therapy reimbursement pathways also in the development stage of the project initiative**. Other significant aspects discussed included:

- need for a practical exchange visit of radiation oncologists of the Baltic States in order to fully discuss the benefits and general treatment workflow of particle therapy;
- need of discussions and direct engagement with relevant government institutions, as well as cancer patient organizations, to raise awareness of the benefits of particle therapy use in cancer treatment.

Lastly, the extended survey and additional data collection for cancer type stratification, clearly showed the **need of well-established national cancer registry**. As for a number of years, such a registry has been lacking in Latvia, good reporting of incidence and mortality metrics for different cancer types is almost impossible. Also, experts from Lithuania mentioned difficulties with their national cancer registry system, discussing improvements that should be made in order to have a well-functioning system. It was agreed between the participants of the workshop that creation and improvements of national cancer registries are crucial for success of such a proposed facility, as these data are necessary in order to make joint decisions between the 3 Baltic States on number of eligible patients, as well as patient referral and reimbursement system functioning.

Speakers: Dr. **Anna Maria Camarda** *(The National Center for Oncological Hadrontherapy (CNAO), Italy)*
Moderator: Dr. **Erika Korobeinikova** (*Lithuanian Society for Radiation Therapy, Lithuanian University of Health Sciences*)

The main and basic gain of particle therapy comes from dosimetric properties due to physical interaction mechanisms – "selective" dose maximum depth – the Bragg peak. With such dosimetric properties clinically there are two main pathways for benefits over conventional photon therapy:

- **reduced dose to organs at risk**, decreasing the radiation induced toxicity probability with same tumor prescription dose;
- **optimized tumor dose escalation for increased local control** probability without increased toxicity risks in the normal tissue.

Furthermore, the gains for carbon ion therapy are also in terms of increased radiobiological effectiveness and possibilities to treat radioresistant tumor due to mitigation of therapy efficacy dependency on cellular oxygen level.

For statistics - there are around **140 particle therapy centers globally** [6], out of which 13 are carbon and 6 multi-particle treatment centers, while the largest portion remains for proton therapy only. Quite a lot of new construction projects are approaching in the coming years.

Though various **international guidelines exist** from sources **such as American Society for Radiation Oncology (ASTRO)** [22]**, as well as United Kingdom** [23] **and Japan** [24] health systems, overall - the **most common indications for particle therapy in the treatment centers are central nervous system (CNS), skull base, head and neck and paranasal sinus tumors**. Further in the session, the European clinical experience from the National Center for Oncological Hadrontherapy *CNAO* (Italy) was shown and discussed with the global picture as well [25].

Firstly, it was shown, that **several clinical indications have enough clinical evidence** of better local cancer control and reduced toxicity with particle therapy treatment, to be included in international guidelines. These indications include **skull base chordoma, chondrosarcoma, and sinonasal carcinoma**. To note, for some of these indications, **particle therapy is already indicated in general cancer management strategy guidelines under "specialized techniques"**. Applied dose fractionation schemes from CNAO experience were also indicated in the session [25].

Proton therapy based **treatment of brain tumors** (as benign or gliomas) and **head and neck tumors gives the benefit of decreased toxicity and improved quality of life**. It is the **treatment of choice for good performance status patients with better survival prognosis** (general factors as age or specific as driver mutations associated with better prognosis, p16 positive, etc.) **with large, irregular shape tumors** or **tumors close to** skull base or other **critical structures**. [26] Furthermore:

- in brain tumors, dosimetric comparison studies have shown **one third reduction in integral dose to whole brain with proton therapy compared to conventional photon based treatments**. **Preliminary clinical evidence** suggests that this dosimetric benefit does translate to a clinical benefit as well, **reducing the neuro-cognitive disabilities** and **increasing overall quality of life** after the treatment.
- for intracranial meningiomas, **proton therapy makes the treatment possible** in large, irregular tumors and tumors in close proximity of brainstem, optic nerves, pituitary gland and cochlea **as such tumors present a therapeutical challenge with conventional photon-based approach**.

- while discussing the glioma treatment, it was indicated that a collaborative group in the Netherlands is working on a development of normal tissue complication probability (NTCP) based patient selection model (*see below*) on basis of neuro-cognitive function impairment [27].
- for head and neck tumors, **proton therapy greatly reduces the dose to critical organs**, while carbon ion therapy could be applied in various radioresistant tumor cases. Clinical evidence findings and overall recommendations were shown for sub-localizations as nasopharynx, oropharynx and sinonasal region, as well as for indications as re-irradiation and postoperative settings. Depending on the localization, **proton therapy can greatly reduce dose to oral cavity, major salivary glands, spinal cord, brainstem and optic pathway, decreasing the radiation induced toxicity profile** [*refer to references within [25]]*.
- radioresistant head and neck tumors as **salivary gland tumors, adenoid cystic carcinoma and mucosal melanoma** were also discussed.

Role of proton therapy was also discussed for management of **ocular melanoma**. Current clinical evidence shows, that **proton therapy offers decreased local recurrence and lower risk of development of cataract and radiation induced retinopathy.** Though particle therapy has shown association with reduced enucleation (removal of eyeball) as well, this association was not statistically significant in the studies. [25]

It is important to note that some of the **radioresistant tumors mentioned may benefit from particle therapy**, specifically, carbon ion, as there is a possibility to increase the local dose without increased toxicity. **These include mucosal melanoma, salivary gland tumors, adenoid cystic carcinoma, as well as spinal chordoma and some soft tissue sarcomas**. There are numerous ongoing clinical trials to prove this benefit. Role of particle therapy was also shown for **treatment of spinal tumors**, as it helps to overcome the difficulties associated with proximity of critical organs. [25]

Upper gastrointestinal tract tumors such as liver (primary hepatocellular carcinoma, cholangiocarcinoma, isolated hepatic metastases**)** and **esophageal cancer** as well as reirradiation of specific tumor sites were also discussed. Although some promising preliminary data suggest that particle therapy may improve the treatment of these localizations, however, there is a **need to wait for the results of ongoing clinical trials in order to increase the evidence**. Role of particle therapy treatment for gynecological malignancies was also shortly discussed. [25]

Clinical evidence and gains of using particle therapy in re-irradiation setting for different localization was also shown and discussed – large and complex recurrent meningiomas, salivary gland cancer, rectal and gynecological recurrences.

Last section of the session was focused on patient selection criteria and models. Generally the selection criteria for particle therapy can be divided in biological and anatomical aspects [*refer to references within [25]]*:

- from biological perspective, high linear energy transfer (LET) radiation like carbon ion therapy should be used for **hypoxic and slowly proliferating tumors**, that have an increased ability to repair DNA damage and exhibit genetic biological micro-environmental features and markers associated with radio resistance. It should also be used in cases, where clinical evidence and knowledge has indicated higher resistance to conventional radiotherapy – **recurrent or highly extensive oncological disease.**
- from anatomical perspective, particularly for proton therapy, **difficult localization** is the key factor – anatomical regions where it is impossible to treat the tumor with curative dose without overdosing the critical organs at risk. It should also be used in

the settings, where surgical resection of the tumors is impossible with negative margin or with physical impairment of critical organs nearby.

As **clinical evidence of proton therapy is clearly still growing**, different patient selection approaches and models were discussed. The global experience suggests that patient selection for proton therapy may be performed in three ways:

- **dosimetric selection** – **comparison of key dosimetrical parameters of critical organs at risk** between optimal proton and conventional photon treatment plans. A **certain threshold for dosimetrical parameter change** is set indicating a favorable choice of proton therapy treatment. An example was given from Denmark for breast cancer patients – if mean heart dose and ipsilateral lung dose-volume constraints can not be reached with optimal photon-based treatment plans, the choice in favor of proton therapy is done [28].
- **normal tissue complication probability models** – essentially is an extension of the latter approach, as the **whole dose-volume data of critical organs is used as input for normal tissue complication probability modelling**. A **certain threshold for reduction of NTCP is chosen**, indicating proton therapy as the favorable modality for treatment compared to conventional photon-based. This approach has been mainly developed and studied in the Netherlands. Key results and aspects [29] [30] [31] [32]:
  - this approach has been **widely studied and used for head and neck cancers**. A particular example for sinonasal cancers was indicated.
  - a study of using this model was shown **for brain tumors** as well, were 11 different clinical endpoints and their associated NTCP was calculated. As mentioned before, **currently a collaborative effort for NTCP model development for neuro-cognitive function impairment is undergoing**.
  - NTCP modelling study data also exists, suggesting even some selected patients with most common cancers as **breast cancer** may have benefit with proton therapy – reduced heart toxicity and risk of secondary contralateral breast cancer.
- Generally, **NTCP model-based approach for patient selection seems clinically attractive, though this approach is largely based on the established and developed NTCP models** – existing data and studies for different clinical endpoints and radiation associated toxicities are necessary.
- overall **cost-effectiveness comparison** of the treatment modalities.

For the future perspective, particle therapy **could also provide clinical benefits in treatment of lymphoma, lung, breast and prostate cancers, though a significant increase in clinical evidence is needed**, as currently the evidence is either conflicting and inconclusive or lacking, in general. [33]

In conclusion, despite the high potential of proton therapy due to physical and dosimetrical characteristics, the clinical evidence supporting the broad use of it is still mixed. It is generally acknowledged to be a safe and effective treatment modality and recommended for many types of cancers - pediatric, ocular melanomas, chordomas and chondrosarcomas. Although new and promising results continue to be reported in the scientific community, increase of clinical study participants is necessary. General consensus of proton therapy community - need to conduct randomized trials and/or collect outcome data in multi-institutional registries to unequivocally demonstrate the advantage of protons.

A key point that was noted through discussions - it is essential to **have state-of-art international registries of patients treated with particle therapy to gain evidence** as clinical trials are complicated in rare cancers. A key starting point for this is **development of**

state-of-art national cancer registries, as these are also largely necessary to **estimate the national cancer epidemiology and treatment capacity for patient selection criteria development**, including the dosimetric and NTCP modelling based selection approaches.

Speakers: Dr. **Maurizio Vretenar** *(CERN)*
Dr. **Elena Benedetto** *(SEEIIST Association, CERN)*
Moderator: Mx. **Taylor Rebecca** (*Imperial College London, CERN*), Prof. **Toms Torims** (*Riga Technical University, Convener of CBG APTC working group*)

The session focused on the core technology for the proposed facility – helium synchrotron – delving deeper into more technological aspects and the associated technology readiness levels (TRLs) compared to the introductory sessions in the bi-lateral Baltic expert meetings in 2022[7].

Shortly re-introducing the Next Ion Medical Machine Study (NIMMS) collaboration, the CERN based collaboration was established in 2019 in the framework of Knowledge Transfer for Medical Applications. Main goal of NIMMS is to build on CERN expertise to **develop a variety of technologies that can be used in a next generation particle therapy facility**, not focusing on a single design. NIMMS collaboration is **mainly working on developing new medical particle accelerator designs to increase compactness of heavy ion therapy machines, while integrating current needs of medical communities and novel, actively-researched therapy delivery methods**. The **focus is mainly on ions "heavier than protons"**, as proton therapy machines are largely commercially available – can not interfere with an international market. As of now the NIMMS collaborations consists of 18 collaborators.

The main rationale of choosing **helium ions** as the design particle for the proposed accelerator lies in the **physical properties** and the **recent re-emergence of interest in helium ion therapy** [34]. As heavier ions than protons, helium ions are less scattered laterally and have reduced range straggling, thus achieving **more conformal dose distributions compared to proton beams** [34]. Helium ions exhibit an **increased linear energy transfer** (LET) compared to protons, therefore **achieving increased biological effectiveness and reduced cellular oxygen level impact on treatment response** [34]. Compared to heavier particles as carbon ions, helium ions undergo **less nuclear fragmentation**, achieving **lesser distal exit dose** and reduced biological effect uncertainties due to the so-called "mixed beam" – different fragment particles contributing to overall dose distribution. Helium ions can be therefore seen **as a compromise of dose conformality and radiobiological effectiveness**, and are now of huge interest in particle therapy community. Clinically, helium ions have been investigated in the early particle therapy studies in Lawrence Berkley National Laboratory [35] [36], while in the recent years – first patient treatment has been done in Heidelberg Ion Therapy Center [37], with plans of starting clinical trials in the coming year. With this re-emergence of interest, **facilities that can experimentally deliver helium ion beams will be of large importance**, in order to perform pre-clinical, medical physics and radiobiology studies.

Looking at the technology needed for radiotherapy, going to heavier and higher energy particles – from conventional photons to protons to carbon ions – involves using increasingly larger, more expensive accelerator complexes [38]. For the mentioned transition "**photons-protons-carbon ions**" a change in particle accelerator itself is needed, respectively "**linear accelerator-cyclotron-synchrotron**" and thus, in addition:

- **increase of the facility size** – on average going from 50 to 500 to 5000 m^2, respectively;

[7] https://indico.cern.ch/event/1229268/contributions/5172905/attachments/2561762/4415647/NIMMS_Estonia_11_22.pdf (*last of bi-lateral meetings)*

- **increase of the accelerator complex financial expenses** – on average going from 1 to 40 to more than 200 million euros, respectively.

Thus, from the scientific research perspective, the design that the NIMMS collaboration is developing is a compact synchrotron facility to fulfil a **compromise between commercial proton accelerators and large-scale carbon ion synchrotrons**:

- increased performance compared to commercial cyclotrons with **reduced radioactivity and beam losses at extraction with more flexible multiple energy operation**;
- **reduced size and footprint** compared to carbon ion synchrotrons, reducing also the technological difficulties.

An important point when comparing the proposed design to commercially available ion therapy synchrotrons, from vendors as HITACHI – **commercial system will not have the flexibility for adaptability of the design, while also not benefitting for training and learning opportunities and local industry involvement in the assembly process.**

The main, key features of the particle accelerator proposed for the facility in the Baltic States [38] [39] [40] [41]:

- synchrotron is designed to **accelerate helium ions to energies corresponding to treatment depth range**, while also providing possibility to **accelerate protons to treatment energies,** as well;
- as the design particle of the synchrotron is helium ion, proton beams can be accelerated to even higher energies **allowing the option of full-body on-line proton radiography**, which is an actively researched imaging method to reduce associated treatment uncertainties;
- synchrotron could also a**ccelerate other, heavier ions (as carbon, oxygen) to energies necessary for biophysical experiments**;
- could be **equipped with** modern delivery methods as ***FLASH***;
- linear accelerator injector part could also be used for **parallel production of radioisotopes for nuclear medicine applications** [42].

Focusing on more technological aspects [39] of the proposed accelerator, as it is a synchrotron, there are actually a lot of similarities even with the large accelerators at CERN as Large Hadron Collider (LHC) – circular construction with a periodic structure of dipole and quadrupole magnets with radiofrequency cavities for acceleration and additional instrumentation for beam parameter measurements. Though unlike LHC, the proposed helium synchrotron is a lot smaller in circumference – only 30 meters compared to the 27 kilometers of LHC – thus, it would not require a designated underground tunnel, but **could be placed in a hospital setting with a footprint of about 2200 m^2**. Another key difference – the LHC accelerator requires continuous operator supervision 24 hours a day during the week, while **helium synchrotron requires simple operation** and continuous control system based supervision as it is a medical machine. The mentioned similarities already highlight that **an expertise within CERN already exists** with circular accelerators similar to the helium synchrotron technology.

Key technical details were discussed and outlined for the various components of the helium synchrotron [38] [39] [40] [41]:

- **ion sources**: **electron cyclotron resonance (ECR) type ion source** is foreseen for the proposed synchrotron. **Either a commercially available source** (for example, from Pantechnik) can be chosen or an advanced one with greatly increased beam current – R&D is still on-going for such one in INFN, Italy.

- **linear accelerator based injector**: **similar design to first modules of linear accelerator based injector at CERN – Linac4**, with the operational frequency of 352 MHz. Linear accelerator based injector is foreseen to be divided modules, providing acceleration up to 5, 7 and 10 MeV/u for helium ion injection, radioisotope production and proton injection respectively. Approach of additional R&D for injector design and operational frequency optimization could also be taken in order to reduce the footprint or costs. Possibility of additive manufacturing technology usage for injector part production was also discussed.
- **injection process into the synchrotron:** addressing the need of medical community, next generation particle therapy accelerators are foreseen to have increased beam intensities in order to perform multi-energy extraction and full tumor irradiation without "synchrotron refilling". Thus **20 times higher intensities are required compared to conventional medical synchrotrons**, which poses a technical challenge and investigations of multi-turn injection approaches are necessary and under going.
- **dipole magnets:** in order to ensure a compact design, **main dipole magnets with flux density of 1.65 Tesla are chosen**, as higher flux density would increase the complexity of the dipoles without a significant reduction in size. The synchrotron lattice would consist of 6 dipole magnets and have a 3-fold symmetry. Furthermore, it was indicated that the mechanical integration will be done in collaboration with the CERN design office with existing expertise in compact synchrotrons.
- **magnets for injection and extraction:** for the injection and extraction process **additional septum magnets are necessary**. **Designs from existing CERN or medical accelerators could be used**, in collaboration with the expert that worked for the systems in two European ion therapy centers – CNAO and MedAustron. Additional work could be done to further optimize the design in order to reduce the power consumption.
- **radiofrequency system: FINEMET radiofrequency cavities** will be used, as they are the state-of-art for low-energy synchrotrons, such as the medical machines, and well-known and used within CERN, offering maximum flexibility in programming functions.
- **beam diagnostics:** beam diagnostics **equipment is to be kept at minimum** to preserve compactness, ensure simplicity of operation and minimizing equipment related downtime while providing all the necessary parameters for monitoring. The accelerator **control system needs to provide** enough **flexibility**, while also **ensuring safety and compliance** with medical equipment standards.
- **extraction mechanisms: slow extraction is to be** used with the synchrotron, allowing beam spills of 1 to 30 seconds. Additional **R&D is currently on-going for slow extraction necessary for delivery on *FLASH* therapy timescales** in less than 500 milliseconds. Radiofrequency knock-out (RF-KO) approach is investigated, with preliminary work indicating necessity of additional hardware development, as the necessary parameters are 10 times beyond currently available capabilities.
- **beam lines:** preliminary design of beam transport lines from synchrotron to treatment rooms is available with the magnetic sequence to ensure the required beam sizes at the patient for different energies. Additional studies could be

done for switching operations between the beamlines in order to improve power consumption and clinical workflow, while ensuring medical standard compliance.

Therefore, it was indicated that **most of the technologies necessary for the helium synchrotron design are already proven and existing**, while additional R&D is mainly necessary for high beam intensity multi-turn injection, multi-energy extraction and *FLASH* timescale slow extraction. **Expertise exists for small synchrotron design and development** with CERN Low Energy Ion Ring (LEIR) [43] and the Extra Low ENergy Antiproton ring (ELENA) [44], with experts from ELENA development team already working in NIMMS helium synchrotron group for the mechanical design of the accelerator layout.

Concluding on the technologies and components necessary for the helium synchrotron [38]:

- **all of the components are quite standard, apart from new hardware necessary for features as *FLASH* therapy** currently standing at TRL Level 5, with additional R&D on-going for some components to reduce the energy consumption and costs;
- **construction** of the synchrotron **consists of integrating parts made in industry**, while taking the responsibility for the overall design, integration, and performance.
- parts of the **initial design can be made at CERN**, with **finalized version done in another institution or in collaboration with industry**.
- as a medical device and the associated required licensing procedures, **medical standard compliance and quality assurance must be taken into account and respected already from initial design stages**. In order to ensure this compliance, while still allowing enough flexibility, a medical licensing expert should be involved in the design process and the project.

Looking in the future, the main goal of NIMMS collaboration for the helium synchrotron is a **complete Technical Design Report.** It is envisaged that it would be available by the end of 2025 [38]**.** This Technical Design Report would be **a public report available for anyone willing to build a medical facility based on the proposed design**. Continued R&D on *FLASH* delivery aspects (slow extraction, dosimetry and delivery), analysis of lattice design and septum magnets, design of synchrotron magnets and analysis and design of other elements (beam diagnostics, radiofrequency systems, dosimetry system) are the necessary research steps for Technical Design Report completion. Mentioned research steps necessitate PhD and masters student involvement, therefore contributions and collaborations from Baltic countries would be highly beneficial.

After the development of the NIMMS Technical Design Report, **the facility interested to develop the technology into a medical treatment center would take the design** – in the perspective of the Baltic States – CERN Baltic Group "Advancer Particle Therapy center for the Baltic States" working group would be responsible. **At this stage, CERN is not to take responsibility of facility**. This would be followed by final design development phase, construction process and commissioning of the accelerator complex. **An important point** throughout the process is the **medical licensing of the device for treatment, thus involvement of medical licensing expert, either a consultant or company, is crucial.** The commissioning process, due to the modularity of the accelerator complex and the various operations made available by the flexible design, can be staged in different parts, making different operations already available earlier:

- firstly, the helium and proton beam form linear accelerator based injector for radioisotope production;
- followed by helium and proton beam commissioning from synchrotron to the experimental area, allowing the start of scientific research programme;

- for use of cancer treatment, medical use certification and commissioning of the proton beam to the fixed beam treatment room;
- afterwards the helium ion beam to the fixed beam treatment room could be commissioned and medical use certification could be acquired. A crucial aspect here – the clinical trials for helium ion therapy itself, which are necessary before the technological certification process. Following the initiatives of clinical trials at Heidelberg Ion therapy center, this aspect could be finished and done there before the construction of the proposed facility.
- lastly, proton and helium ion beams would be commissioned for use in the gantry based treatment room.

As mentioned, CERN is not taking responsibility for the final design, construction and commissioning process, though following the model that was used with development of MedAustron ion therapy center in Austria, an agreement could be possibly negotiated with the CERN management for expert support with the final design and component procurement process, against a financial contribution.

In conclusion, with the presented material a lot of fruitful discussions took place and important points were made, which can be summarized as:

- the **NIMMS helium synchrotron design provides vastly larger customizability** compared to a commercially available system offering:
    - **flexibility and adaptability** throughout the final design and construction process, as well as beyond, to the new delivery technique developments based in radiobiology research;
    - **modularity** as the components of the accelerator complex are separate in construction process and assembled by facility itself, both conventional and commercially available components in the market can be used, as well as newly developed components through R&D to match the specific need of the end user;
    - **multiple benefits** as the facility of such design goes **beyond just cancer treatment**, **also including radioisotope production** for nuclear medicine, **infrastructure for scientific research** and most importantly – **teaching and sharing of expertise within the Baltic States** in the field of particle accelerators.
- as also agreed by the experts from the Baltic States **such a design offers more than a commercial**, for example – HITACHI synchrotron, **technology**, as the facility is freely adaptable throughout the process, fine-tuning the parameters and training new experts in the Baltic States, preventing the "brain-drain". The role of adaptability can be seen from other European ion therapy centers, as even know both CNAO and MedAustron are adding new ion sources and extraction techniques for delivery.
- such a smaller accelerator complex can even prove to be more interesting and facilitate more creativity than large complexes, furthering the importance of training people.
- a lot of discussion took place on **helium ion therapy itself** – as it seems appealing from physics point-of-view, is it really of clinical interest for cancer treatments. Initial data of clinical helium ion therapy use have been shown from the data of Lawrence Berkley National Laboratory and from the physical properties, **it really seems appealing as evolution** (*not revolution*) **of proton therapy**. Of course, it does seem natural going in the future to develop novel, cutting-edge technologies, even more so from ethics perspective – **patients**

should always receive the best option for their treatment. The biggest challenge is the **synergy between the cutting-edge technology and the end users – radiation oncologists.** "How open are end-users to a change?", "Is there really enough advantage of helium ion therapy to change the clinical workflow" – are the questions that will pose the challenges in the future. Even from the experience of another European ion therapy center CNAO – even carbon ion therapy is hard to accept in radiation oncology community, as the trust in it is based just on studies from Japan.
Despite that, the other medical perspective – it is a rapidly developing field, having new technologies and even new approaches, thus the field of medicine is always open find ways to prove novel technologies.

- as helium ion therapy is still under discussion in medical community, it must not be forgotten, that **facility will offer clinically well-established proton therapy from "day one"**, therefore there will be no clinical use delays after the commissioning process is done.
- speaking about delivery methods, there is a large interested in radiation therapy community on the ultra-high dose rate delivery – *FLASH* therapy. Though this aspect must also be taken with care, as there are a lot of unknowns of this delivery method and the underlying biological mechanism of the effect itself. Therefore, currently there exists a lack of precise numerical requirements needed for technology development.
- with the proposed helium synchrotron complex, **there should be a large focus on the scientific research aspect** with the experimentally dedicated beamline. As mentioned, the proposed facility could also be able to heavier ions such as carbon and oxygen to energies corresponding to a range of about 12 centimeters in water – enough for radiobiological and other experiments. Thus the **research aspect of the machine is crucial** as it allows studying new ions for therapeutical purposes, building a new research community and training the future generation. The priority should truly be a **multi-disciplinary research** unifying fields of physics, biology and clinical medicine. Furthermore, the facility should be **opened up to other industries for additional R&D projects,** as a lot of different research fields could benefit from an irradiation facility.

Speakers: Prof. **Maija Radzina** *(University of Latvia, Riga Stradins University, Latvian Radiology Association)*
Mr. **Edgars Mamis** *(University of Latvia, CERN)*
Moderator: Dr. **Diana Adliene** (*Kaunas University of Technology, Vice-convener of CBG APTC working group*)

As indicated in previous session – the proposed core technology of helium synchrotron would include linear accelerator based injector, which could be used for a parallel production of radioisotopes for use in nuclear medicine. Thus the focus of this session was:

- identifying the current trends of nuclear medicine within Europe at large;
- identifying the current status of nuclear medicine field within the Baltic States;
- discussing main scientific research directions of different aspects of nuclear medicine;
- discussing about the synergies between the proposed radioisotope production within the facility and the existing infrastructure in the Baltic States.

Thus the reports in session were given in two parts – report on European trends and Baltic States status of nuclear medicine from perspective of PRISMAP project [45] and report of scientific research directions from the experience of CERN MEDICIS experiment [46].

PRISMAP is the European medical radioisotope programme focused on production of high purity isotopes using the technology of mass separation. The report in the session is given from the perspective of Working Package 5 “Industrial and clinical collaboration” – deliverable “Questionnaire on industrial and clinical key players and needs” [47]. The questionnaire included in **total 114 respondents from 30 European countries and 104 different institutions** divided in **3 groups – manufacturing facilities, research institutions and end-users – both pre-clinical and clinical**. Division of the respondents between the 3 groups was 16, 48 and 40 respondents, respectively. Next paragraphs separately focus on the different findings reported from each of the respondent groups.

Focusing on the production of radioisotopes both from manufacturing facilities and research institutions [47]:

- **most commonly produced radioisotopes** in these facilities, addressing the clinical and scientific research needs, are **^{68}Ga, ^{18}F, ^{99m}Tc, ^{11}C, ^{64}Cu, ^{161}Tb, ^{177}Lu, ^{67}Cu, ^{89}Zr, ^{52}Mn, ^{123}I, ^{124}I, ^{188}Re, ^{90}Y, ^{225}Ac, ^{67}Ga, ^{165}Ee, ^{233}Ra, ^{44}Sc** and others.
- there exists an **increasing demanding for alpha emitting radionuclides**, **particularly ^{225}Ac** – a highly important and open objective is to **identify more sites that could offer such radioisotope production**.
- focusing on radioisotope distribution challenges within Europe, mainly regulatory limitations, customs clearance, lack of harmonized legislation for distribution, complex supply chains and licensing issues were mentioned. Therefore, these challenges should be thought of and addressed at the Baltic States scale, if such a unified facility would be used for radioisotope production.

Focusing on scientific research perspective [47]:

- as 80% of respondents indicated that their R&D activities would benefit from collaboration like PRISMAP project, indicating that **large scale collaboration is of uttermost importance in the fields of novel radioisotope production and nuclear medicine** – such approach should be taken into account for developments in the proposed Baltic States facility as well;

- as for equipment necessary for nuclear medicine research both in pre-clinical and clinical setting, **most of the respondents have indicated having** animal single photon emission computed tomography unit with integrated computed tomography **(SPECT/CT) or** magnetic resonance imaging **(SPECT/MR),** as well as animal positron emission tomography unit with integrated computed tomography **(PET/CT) or** magnetic resonance imaging **(PET/MR)**. Less in numbers, but most of the facilities also have experimental long term animal facilities for follow-up after radiation exposure, as well as clinically usable PET, PET/CT or PET/MR and SPECT, SPECT/CT or SPECT/MR.
- main **radioisotopes identified as of interest for research** in the following years are ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{161}Tb, ^{225}Ac, ^{89}Zr, ^{67}Cu, ^{64}Cu, ^{165}Er/^{169}Er, ^{47}Sc, ^{44}Sc, ^{177}Lu, ^{211}At and ^{188}Re.

Focusing on end users in nuclear medicine field, both in clinical and pre-clinical setting [47]:

- **most commonly used** radioisotopes currently are **^{177}Lu, ^{68}Ga, ^{111}In, alpha emitting isotopes, ^{225}Ac, ^{64}Cu, as well as isotopes from terbium and scandium families**;
- in a **2 to 5 years time**, the end users foresee most common use of **^{225}Ac, ^{64}Cu, ^{68}Ga, ^{177}Lu, alpha emitting isotopes, terbium family isotopes, ^{90}Y, ^{111}In** and lastly – **scandium family isotopes**;
- for the novel approach of theranostics (simultaneous diagnostic imaging and targeted therapy) **none of responding institutions have yet indicated an interest of possibilities of "matched pair" radiopharmaceuticals offered by radioisotopes such as Tb, Y, Cu and Sc in the near future**. Most likely this reflects the **insufficient pre-clinical data of effectiveness of such approach**, as well as **general lack of access or availability to such exotic radioisotopes**. Usage of peptide and PSMA based radiopharmaceutical pairs of ^{68}Ga, ^{177}Lu, ^{64}Cu, ^{18}F, ^{99m}Tc and others are more common approaches for theranostics use;
- **general interest** has been indicated **in new radioisotopes and radiopharmaceuticals** for research and pre-clinical and clinical purposes as well as **novel technology development**;
- main clinical and pre-clinical research areas have been indicated to be nuclear medicine applications in the fields of oncology, cardiology, infection and inflammation, endocrinology, neurology;

To give the perspective of status of nuclear medicine in the Baltic States, answers were extracted from PRISMAP questionnaire data, as well as additional data from other studies were used. In total, data from 7 respondents from the Baltics were present, one of which is a manufacturing facility. Some of the key metrics, characterizing the status in the Baltic States are summarized [48]:

- **nuclear medicine diagnostic equipment in the Baltic States** accounts for a total of **14 SPECT and 8 PET units**, without the additional inclusion of gamma cameras [11][48];
- as for **radioisotopes of diagnostics purposes**, all facilities are using **^{18}F** with most of the facilities using also **^{99m}Tc**, and two of the centers – **^{123}I**;
- as for **radioisotopes of therapeutical purposes**, most of the facilities are using **^{177}Lu**, as well as **^{223}Ra** for targeted alpha therapy, two of the centers are using **^{131}I**, while East Tallinn central hospital uses radioisotopes as **^{90}Y, ^{186}Re, ^{89}Sr and ^{153}Sm**;

- for theranostics approaches, **mostly [^{18}F]PSMA-[^{177}Lu]Lu-PSMA** is used, **none of the novel matched pairs are currently used**, apart from well established ^{123}I-^{131}I.
- main nuclear medicine clinical applications are in the fields of oncology, cardiology, neurology, infection and inflammatory response diagnostics, endocrinology, traumatology, nephrology, pulmonology and gastroenterology, with **extended focus of expanding oncological application in the near future of 2 to 5 years**;
- **common future interests** in radioisotopes among Baltic States respondents included more-widespread usage of **^{177}Lu** and introduction of **^{68}Ga, ^{64}Cu, ^{225}Ac and terbium isotopes**. For **theranostics approaches, gallium-lutetium pairs** are of future interest, where novel use of ^{64}Cu could provide an appealing alternative for ^{68}Ga due increased half-life time and spatial resolution;

A very important point to consider for developing parallel radioisotope production in the proposed facility is synergy with existing infrastructure in the Baltic States. Currently, a **manufacturing facility exists in Latvia** under Nucleo, Ltd., while there is also an **on-going construction of a cyclotron facility in Lithuania** as part of Clinic of Kaunas [48]. Both of the facilities are to use **commercial, low energy cyclotrons**, therefore focusing on production of most common radioisotopes necessary for diagnostical nuclear medicine – **^{18}F, ^{15}O, ^{11}C and ^{13}N,** as well as using generators for production of **^{68}Ga**. Also, the future manufacturing programme extension plans are similar, focusing on **scandium, copper** and **terbium isotope production**. Thus the key-point to consider for development of parallel radioisotope production within the framework of proposed facility – **it should focus on complementary production for the existing manufacturing facilities without competition and overlapping**. The focus should therefore be on low production quantities of diagnostic isotopes necessary just for functional imaging necessary for radiotherapy treatment planning and treatment response assessment patients of cancer patients within the facility, while in terms of larger export focusing on **non-conventional and complementary isotopes of interest in the community**. These would include isotopes of more efficient production pathways using linear accelerators not cyclotrons.

Second part of the session mostly focused on the possible research pathways in nuclear medicine and radioisotope production from the experience gained in CERN MEDICIS experiment [49]. MEDICIS facility contributes to medical research by production of novel radioisotopes, while also using the mass separation technology. Apart from diagnostics aspects of nuclear medicine, the role grows also for targeted therapies using alpha and beta(-) emitting isotopes, which have shown clear results in treatment of even metastatic cancer. Purity of medical radioisotopes is of utter most importance in nuclear medicine applications, therefore both **radiochemical separation** and **isotopic separation** using **mass separation technology** are used [49]. Mass separation technology allows unique opportunities for some radioisotopes, therefore it was **discussed and suggested that inclusion of mass separator within the facility for novel radioisotope production could be considered for future developments**.

Research directions from MEDICIS experiment were shared and are summarized as [49]:

- scandium family isotope production from titanium and vanadium targets with proton beams [50][51];

- throughout the years, production of various radioisotopes of interest have been studied in CERN MEDICIS facility, including **terbium and scandium isotope family, actinium-225 and actinium-227, isotopes of thulium family, samarium-153, isotopes of platinum** and others [52].
- as the proposed helium synchrotron technology could use helium-4 beam for radioisotope production, a **production route of scandium-47 from calcium targets** was discussed [53]. Production of **terbium isotopes** with a helium-4 beam could also be possible [54][55].
- focusing on alpha emitting isotopes:
    - although astatine-211 is attractive from perspective of it's physical properties in application targeted therapies, **the production route must be carefully considered as astatine-210 is co-produced**, that can have detrimental effects on overall effectiveness [56][57];
    - currently, **no cross-sectional data are present for actinium-225** production with helium-4 beams [58][59];
- for production via the helium synchrotron technology isotopes from **scandium, copper and terbium families** can be considered, as well as **actinium-225, gallium-68, lutetium-177** and others;
- radioisotope production is just one part of radiopharmaceutical manufacturing, a **large scientific research direction** could be in the **developments of radiochemistry field** – radionuclide chemical purification method development, labelling studies for pharmaceutical development as well as optimization of synthesis methods;
- facility can also be used for **nuclear reaction cross-section measurements** either for refinement of existing data or characterization of new target materials. A unique opportunity is the use of helium ion beam, as cross-section data are more sparse for such type of nuclear interactions. Development of such a scientific research pathway would also involve development of **nuclear physics within the Baltic States**.
- further developing on previous point, facility would allow specific radioisotope half-life measurements for existing data refinements, as well as spectroscopy studies for purity characterization studies;
- lastly, recent finding with large interest of **samarium-153** use were shared [60][61].

Following the shared reports, discussion took place mainly focused on **activities to be done at current stages and pathways for joint efforts in nuclear medicine field in the Baltic States at large**:

- **a larger focus in nuclear medicine should be given for targeted therapies**, not just for functional imaging of PET and SPECT, as such a similar diagnostic information can now also be deduced from such modern imaging modalities as spectral computed tomography imaging or specific magnetic resonance imaging sequences;
- as mentioned before, **it is crucial to understand and define the role of the parallel isotope production in the helium synchrotron complex in terms of Baltic States infrastructure at large** – it should not be positioned as a competitor with the existing manufacturing facilities, overlapping for production of common-use diagnostic isotopes. **Focus** of the helium

synchrotron facility should be **non-conventional isotopes that are not easily produced with the low-energy commercial cyclotrons**, because of their limited energy reach and use of heavier particle beams for production.

- **cooperation among the nuclear medicine societies and manufacturers in the Baltic States** should be strengthened, if such a large scale collaboration as the facility like the one proposed is to be made – networking activities, balancing the production amounts of most commonly used radioisotopes, avoiding overlaps of non-conventional isotope production, as well as sharing information about novel isotope production possibilities.
- as larger quantities of radioisotopes and possibly – non-conventional, specific radioisotopes – could be produced, **possible export pathways should also be considered** as part of the business plan – if the Baltic States together could be able to produce more than is necessary for internal use, how still to benefit from this option.
- as preparatory activity and advancement of nuclear medicine scientific research at large - **trying to explore the existing cyclotron facilities for research activities** beyond commercial production – investigation of novel radioisotope production;
- in order to expand the know-how and train new experts in the field, it is important to **raise the awareness and interest for participation and joining in CERN MEDICIS projects**;
- **common points between the Baltic States research institutions should be established** in field related to particle therapy and related technology developments at CERN, as well in the fields of nuclear medicine, specifically targeted therapies;
- more **inputs** are needed **from nuclear medicine and radioisotope production field experts** from the Baltic States and Europe at large;
- for such a large scale facility, an **increased number of nuclear medicine specialists is necessary - radiochemists, radiobiologists, specialized medical physicists, etc. Training aspects of these specialists should be already considered at this stage of the initiative.**
- needs identified in the PRISMAP questionnaire for development of daily clinical practice should also be considered as aspects necessary for such a facility - database of available radionuclides, on-site training with international experts, as well as outsourced training for medical doctors, medical physicists and other medical and technical personnel.

Educational necessities and possible solution pathways for clinical and technical personnel training

Speakers: Dr. **Manjit Dosanjh** (*University of Oxford, CERN*)
Dr. **Erika Korobeinikova** (*Lithuanian Society for Radiation Therapy, Lithuanian University of Health Sciences*)
Mr. **Kristaps Palskis** (*Riga Technical University, CERN*)
Moderator: Prof. **Andrejs Erglis** (*University of Latvia*)

The final session focused on one of the key concerns and discussion points posed within the bi-lateral Baltic expert meetings in 2022 – training and additional education is necessary and crucial to create a core expert team running such a novel facility. Thus the session was given from two perspectives:

- overall personnel statistics within the Baltic States and discussion on some of the needs from clinical radiation oncology and medical physics side;
- experience from European perspective on projects related to expert training and capacity building within the field of particle therapy.

The reported personnel statistics data [62] in the Baltic States were collected in 2022 in the Access to Radiotherapy Technology (ART) study [10], already mentioned in the first session. In general, looking at the conventional radiotherapy, the core team consists of **radiation oncologist, radiation therapy technologist (RTT,** *often referred to as radiologist assistant in the Baltic States***) and medical physicist**. Within each of the countries there are

- 10 to 40 **radiation oncologists** per country – **about 85 in total** for all 3 countries;
- 30 to 50 **radiation therapy technologists** per country – **about 130 in total** for all 3 countries;
- 20 to 30 **medical physicists specialized in radiation therapy** per country – **about 65 in total** for all 3 countries.

Thus, overall each of 3 Baltic countries has a core specialist team of close to 100 people per country working in conventional radiation therapy. Looking further, a lot of other specialties are also involved in radiation therapy such as technical support engineers. Considering the multiple functions of the proposed facility, also nuclear medicine related specialties are relevant. Though, the mentioned specialists are all **specialized in conventional photon radiotherapy using commercial linear accelerators**. This opens the question – "what knowledge and additional specialties are needed to specialize from conventional photon radiotherapy to particle therapy?"

Before delving deeper in the additional educational needs, firstly the available academic educational programmes for the core radiotherapy specialties were discussed [62]:

- **all three of the Baltic States offer academic degree programmes** for these core specialties at different levels;
- **dedicated residency programmes exist for radiation oncologists** (*therapeutic radiologists*) in all three countries;
- college and bachelor level degrees are offered for radiation therapy technologists in all three countries, with dedicated master's degree programme offered also in Estonia;
- **academic degree in medical physics** is possible with inclusion of the **PhD level** in all 3 countries, though it must be noted **that a dedicated, official clinical residency programme for medical physicists does not exist yet** as it is the common practice in Western European countries;
- a lot of specialists are actively engaging in European radiation oncology related organizations and societies, such as ESTRO and EFOMP;

- focusing on furthering the knowledge, specialists try to engage in dedicated ESTRO and IAEA organized educational courses, though it must be noted that **state-supported funding is limited, thus sometimes limiting the number of participants able to take part in the courses.**

With the general statistics laid out, the focus was then put on discussion – what would be the additional education needed for developing skillset necessary for particle therapy practice? Firstly, **medical physics and general technical perspective** was discussed [62]:

- the changes and nuances of **differences in treatment planning and quality assurance procedures** of particle therapy could be acquired in **exchange visits with European ion therapy centers** and specialized further knowledge educational courses**;**
- as the underlying physics processes of particle therapy are more complex and usually better understanding of treatment planning system (TPS) algorithms is necessary – **role of linear energy transfer modelling, relative biological effectiveness calculations** and **general use of Monte Carlo** simulations for physics process modelling in particle therapy **should be a focus of additional education courses and could be possibly be incorporate in an university curriculum**;
- due to lower number of particle therapy centers in the world compared to conventional radiotherapy, **focus** should also be given **on skills** (*physics process modelling, programming*) **necessary for a local treatment planning system creation** or **close work with commercial vendors for novel developments** necessary for particle therapy deliver methods under research;
- due to the role of relative biological effectiveness modelling in particle therapy, **bigger role and integration of radiation biologists into clinical workflow** would be necessary;
- as the proposed helium synchrotron would be **assembled by the facility itself**, training of **on-site accelerator physicists and engineers is crucial for operation** of such a machine;
- continuing on the previous point – **the general technical paradigm of such a facility would be completely different from a conventional radiotherapy center** – it is not a commercial machine, thus the full responsibility of ensuring continuous operation, repairs and periodic maintenance is the **responsibility of the on-site personnel**.
- further focusing on technical specialties involved in the facility, **specialists in information technologies** (IT) would be necessary with specializations in applications **for medical data analysis**, big data, oncological data systems and medical physics. It was noted by Kaunas University of Technology representatives that integration of IT applications will be integrated in medical physics study programmes in coming academic years.

Focus was then put on the needs from **clinical aspects** of translation from conventional therapy to particle therapy with key points discussed:

- **development of state-of-art cancer registries** is of uttermost importance for the success of such a facility;
- due to the long term of the project, it was discussed and proposed that even at the **early stages of the project two networks should** be considered and **made – clinical and scientific networks**;

- aspects of **education on proton and particle therapy could be included into academic curriculums** of RTT programmes, radiation oncology residencies as well as medical physics academic degrees. As a positive example in the region – particle therapy has been already introduced as one of the study courses in Medical Physics Master's degree program at Kaunas Technology University (KTU);
- increasing the **number of vacancies for radiation oncology residency** should be considered;
- *hands-on* and **long-term exchange visits** would be necessary for education on **practices in particle therapy centers** for radiation oncologists and RTT, as well as nuclear medicine specialists in relevant centers;
- **development of close collaboration network**, including global experts, for **preparation of the protocols** both for indications and treatment methods (*both in particle therapy and nuclear medicine*)
- involvement of **political structures for development of straight-forward and clear reimbursement schemes** for all the novel diagnostic and therapeutical procedures the facility could offer;
- focusing more on education of other communities, **discussion with patient communities and organizations** should be considered for spreading awareness of the role of particle therapy in cancer treatment;

Basic needs for developing a scientific community in the Baltic States were also discussed [62]:

- the project of such a scale clearly needs **strong, creative and innovative leaders**;
- the scientific network formed in the Baltic States should be **integrated in larger networks both at European and global scales**;
- **visiting scientists from outside the Baltic States** should be involved in participation in various scientific programs of the facility to further expand networking and global collaboration;
- as the facility would focus on pre-clinical and clinical research as well, **educational activities** within the scientific network would be necessary **on clinical trial design, organization**, ethical issue considerations and associated legal procedures.

Lastly, the educational needs for specialists in nuclear medicine were also discussed and have already been largely summarized in the previous chapter of this report. An additional notes can be made:

- regarding specialized knowledge in particle therapy – it was mentioned and discussed that actually **there are no dedicated university undergraduate or graduate programmes with the only focus on particle therapy –** knowledge base in particle therapy is usually given in **further education courses**, such as the ones provided by ESTRO [63] or educational sessions during the PTCOG annual conference [64];
- regarding **the long term exchange visits of specialists** at particle therapy centers – in another, following workshop [65] this aspect was discussed as well and the expert opinion from particle therapy centers suggest **a period of at least 6 months working in particle therapy** to learn additional knowledge and differences in the workflow compared to conventional radiotherapy;

These aspects should be taken into account for development of further activities related to personnel education.

After reporting and discussing the statistics and possible needs of the Baltic States, European experience for similar settings was discussed. As was mentioned in the first chapter, in 2002 the European Network for Light Ion Hadron Therapy (ENLIGHT) [66] was established for coordination of joint European developments in particle therapy. The idea for such a thematical network was submitted as a **proposal to European Commission** for funding. ENLIGHT network had many goals including knowledge and best practice sharing and harmonization of data, while from the inception of the network, one of the **key goals was provision of training and education**. Furthermore, 4 different projects later developed "under the umbrella" of ENLIGHT network were discussed as examples of possible pathways for the Baltic States:

- PARTNER project [67] – **Marie Curie Initial Training Network** based project that included 12 institutions, including 29 participants with the **main aim of the project – creation of the next generation of experts** in various particle therapy related fields – physicists, clinicians, biologists and engineers.
- ULICE (*Union of Light Ion Centres in Europe*) [68] – project that provided a successful **transnational access to beam time** at Heidelberg Ion Beam therapy center and CNAO, while also providing **training courses at these facilities** – both for clinically practicing clinicians and physicians in radiation therapy, as well as for researchers for experimental beamtime access.
- ENVISION (*European Novel Imaging Systems for Ion Therapy*) [69] – participants from 16 leading European research centers and industrial partners with main aim of **R&D in real-time medical imaging** for more effective and precise particle therapy treatment;
- ENTERVISION [70] – **Marie Curie Initial Training Network** based project including 12 institutions with 16 trainees focused **on development of network of medical imaging expertise** with applications in particle therapy.

Summarizing the reporting on the mentioned projects, ENLIGHT network and involved community has always recognized **the high importance of young scientist and medical doctor training**, considering it as **one of key priorities** – as the number of particle therapy centers increase globally **the necessity for specialized staff for operation** becomes more and more important. Furthermore, the ENLIGHT network has a regular meeting annual meeting, which includes **1 to 2 days** long open training course. The **possibility to have an ENLIGHT network meeting in the Baltics was discussed** as a unique and beneficial training option.

The previously mentioned approaches for capacity building oriented projects **are long-term, focused on larger community development**. For immediate actions on training, knowledge base and skill expansion, some already existing European training opportunities were discussed and reported:

- a lot of opportunities are provided by HITRI*plus* [71]:
    - **specialized courses** focused on both the scientific, technological and physics aspects as well as clinical aspects with **recordings freely available on-line** [72][73][74];
    - **transnational access** – **opportunities for clinical teams to visit European ion therapy centers** for experience exchange, as well as beamtime access for various scientific research [75];
    - **regular webinars** on various topics related to different particle therapy delivered by key experts representing the European ion therapy centers and scientific research facilities.

- ***The Hadron Academy* PhD course** delivered by CNAO open for applicants throughout the Europe interested to work in various research projects related to both technological and clinical aspects in particle therapy development [76].

Summarizing the proposed activities and European experience throughout ENLIGHT community and associated projects, the key considerations for development **of large scale, multi-centre R&D and training collaborations**:

- close collaboration with international organizations as ESTRO, EORTC and other groups;
- development of joint basic and translational biology and physics research oriented at particle therapy developments;
- joint clinical research activities and patient model developments;
- joint efforts and developments of educational activities and training courses.

As the topic of education is of high importance in the further developments of this project initiative, a lot fruitful discussion took place and ideas were proposed, which are summarized as:

- based on the mentioned experience in **Marie Curie Initial Training Network** projects, it was agreed by the Baltic community experts that such an **approach would be highly beneficial** for training necessary of experts for operating the facility. **The proposal** for such a Marcie Curie Initial Training Network project **should be submitted** in early stages of the project, most likely alongside with a feasibility study of the center. **Idea of such an approach was well supported by the participants**.
- **clinical team** – radiation oncologist and medical physicist – professional **exchange visits under HITRI*plus* project transnational access** opportunities to European particle therapy centers are of high importance – such visits would give greater insights of treatment workflow specifics and hands-on experience in particle therapy. **Long term exchange visits** for educational training need to be definitely considered **at later stages** of the project initiative.
- **ENLIGHT community meeting in the Baltics** should be considered as it would provide a highly beneficial training and networking opportunities for local specialists;
- a possibility of having **monthly education seminars** with possible involvement of ENLIGHT community experts for the Baltic States was also discussed and seen as a good option;
- **discussions and information sharing at earlier stages of education** should be considered as it is a long-term development project. Possibilities of radiation therapy and particle therapy master classes should be considered at high school student level, while some additional educational seminars and/or course could be provided at undergraduate level **to build general interest in STEM subjects, with particular focus on subjects involved in the proposed activities at the facility**. Seminars could also be oriented towards at student further education group and organizations – both in physics and clinical medicine.
- **involvement of Baltic scientific universities and research institutions in various CERN medical applications oriented projects**, as well as other European scale initiatives and projects should be strengthened for expertise development.

Overall conclusions

The "*Advanced Particle Therapy Center in the Baltic States"* is foreseen as a major research infrastructure with applied scientific programme, active technology development, educational value as well as clinical functions at the core of the activities. Therefore, one of the key enabling factors of the initiative as a whole is - **demonstration of a clear support from Baltic medical communities**. This aspect is key for further developments, as the clinical function of the proposed facility is the central one. Hence analysis of the available supporting facts and evidence on a medical case in the Baltic States for particle therapy was one of the key goals of the workshop. By summarizing the outcomes of each of the workshop sessions, number of key findings became evident from the view- point of the medical case.

I State-of-play

1. For the Baltic region as a whole, current practices of conventional photon based radiation therapy:
    - 1.1. medical linear accelerator availability is within international recommendations and guidelines from IAEA [13] [14];
    - 1.2. modern radiotherapy techniques as intensity modulated (IMRT) and volumetrically modulated radiation therapy (VMAT) are practiced, along stereotactic techniques (SRS and SBRT), with specialized machines such as robotic radiosurgery unit and linear accelerator with integrated magnetic resonance imaging;
    - 1.3. for future developments, diagnostic imaging units specific for radiotherapy planning would be necessary.
2. Cancer incidence and mortality statistics in the Baltic States for different cancer types are following the global trends [11] [15].
3. With a total of 6.02 million inhabitants in the 3 countries, the crude cancer incidence and mortality rate is 632 and 297 per 100'000 inhabitants, respectively. In 2020, out of all cancer patients **13045 had received radiation therapy treatment**, which accounts for about 35 % of the patients [11].
4. Throughout the years, various study groups have investigated and created general guidelines for number of patients eligible for particle therapy [7] [16] [17] [18] [19] [20]. Findings in these reports, generally indicate that **between 1.5 to 15 % patients receiving conventional radiation therapy would be eligible for particle therapy. In the case of the Baltic States, it would in total account for about 500 to 2000 patients annually**. Such a number can be deemed sufficient for a two room facility, as about 200 to 500 patients per room are treated in particle therapy centers globally [21].
5. Initiative for further investigations on Baltic data of cancer incidence and treatment statistics specific for application of particle therapy is being performed and initial results collected are generally promising for a perspective of particle therapy center [11].
6. Undoubtfully, further **development of state-of-art cancer registrie**s will be crucial for such a large scale multi-national research infrastructure - treatment center, especially as far as patient selection is concerned.

II Clinical perspective of particle therapy

7. It is known that, particle therapy offers two pathways of benefits – reduced radiaton induced toxicity with same dose prescription or optimization of increased local control by dose escalation without increasing adverse effects. It must be noted, that in recent years it has been discussed within the particle therapy community that a larger focus could be put on the second aspect, as indicated also in the findings reported at this year‘s PTCOG conference [64]. While main focus of particle therapy has been the reduction of radiation toxicity, future applications in cancer types with poor local control rates could increase, such as non-small lung cancer, esophageal and pancreatic cancers and others.
8. Particle therapy has been clinically established as highly beneficial modality in treatment of various central nervous system (CNS), skull base, head and neck and pediatric cancers with increased treatment outcome with reduced adverse effects and overall increase in quality of life. Highly promising results have also been shown in treatment of ocular melanomas, liver cancer and others [25].
9. When considering heavier ions than protons for particle therapy, particle therapy applications in treatment of various sarcomas and radioresistant head and neck tumors have also shown clear benefits over conventional radiation therapy [25].
10. Currently there are series of on-going clinical trials on proving particle therapy efficiency in treatment of other cancer types, including more common localizations such as lung, breast and prostate, to further expand the clinical evidence base [25]. Findings in the PTCOG conference [64] have also indicated level-1 evidence in several cases and number of clinical trials increasing like never in the past.
11. With the sometimes limited clinical evidence base and discussions of particle therapy use cost effectiveness, various approaches for patient selection have been proposed such as dosimetric parameter comparison and full cost-benefit analysis on patient base, with the greatest promise in the model based selection approach developed by the Netherlands by estimating reduction of normal tissue complication probability. Such model based selection approach has been mainly studied for head and neck and brain tumors, with a lot of effort on-going for developments for other cancer types as well [25] [28] [29] [30] [31] [32].

Focusing on the clinically relevant subjects discussed in the workshop it also must be stressed that a development of particle therapy as another cancer treatment modality in the Baltic States **should not be seen as a competitor to the existing conventional radiotherapy infrastructure but rather a complimentary method** to increase the treatment outcome and patient **quality of life** in cases of specific cancer types.

III Technological aspects

As indicated, during the bi-lateral meetings [77] [78] [79] at the end of 2022, concern was put forward also regarding the technological readiness level of the core technology of the proposed accelerator complex – the helium synchrotron. During the workshop, the concern was addressed, while also providing more in depth technological information along with future development strategies [38] [39] [40] [41]. Key conclusions:

12. Compared to commercial proton therapy cyclotrons or even heavy ion synchrotrons (*as offered by HITACHI*), the proposed NIMMS helium synchrotron design would provide larger flexibility and adaptability of the design towards new delivery techniques, modularity for various different functions and training and *know-how*

expansion possibilities in the field of accelerator technology as the complex is *self-assembled*. Such an approach to the accelerator complex also provides larger freedom for scientific research capabilities.

13. Most of the technologies used within the helium synchrotron are well-known, established and with vast expertise and knowledge-base at CERN, thus greatly reducing the associated risk with R&D activity necessity. R&D activities would be necessary only for use of novel delivery methods as *FLASH* or for power consumption optimization of some of the components.
14. Part of the components necessary for helium synchrotron are commercially available, while dedicated manufacturing is necessary for others, providing clear pathways for Baltic industry sector involvement.
15. NIMMS Technical Design Report (TDR) outlining the proposed accelerator technology is envisaged and could be available by the end of 2025 [38].
16. Throughout the process, starting already from early design stages, involvement of medical device certification and licensing expertise is necessary, to ensure compliance to standards and minimize problems in later stages.
17. The modularity of the design allows a staged commissioning, providing research and clinical use of some of the functionality of the accelerator even before full commissioning process is done;
18. With the various functionality offered by the proposed accelerator, a large focus should also be made on the multi-disciplinary scientific research pathways such a facility would provide.

IV Parallel radioisotope production perspective

The helium synchrotron technology provides possibility of parallel radioisotope production with linear accelerator – a novel technology that could have large benefits in production efficiency of certain non-conventional isotopes compared to commercial production methods. Throughout the discussion in the bi-lateral meetings at the end of 2022, interest of Baltic nuclear medicine community in the project was indicated, with the needs to understand the possible synergies. European trends and Baltic region status in nuclear medicine, as well possible research pathways were reported and discussed in the workshop and are summarized as [47] [48] [49]:

19. While currently, most commonly non-conventional isotopes are gallium-68 and lutetium-177, a large, European scale interest in use of radioisotopes applicable for theranostics (copper, scandium and terbium isotopes) and target therapies, especially with actinium-225, for the near future was reported [47] [48].
20. From the Baltic perspective, future interests are similar to European, with focus on lutetium-177 and clinical introduction of gallium-68, copper-64 and terbium isotopes, as well as targeted alpha therapy with actinium-225 [48].
21. Nuclear medicine procedures are currently used in various clinical application in the Baltic States, with reported interest to increase oncological applications in the near future [47].
22. With two potentially functioning manufacturing facilities in Latvia and Lithuania in the near future, radioisotope production within the region should clearly be harmonized and synergized between these institutions and proposed accelerator facility to avoid overlaps and over-production, while defining also clear radioisotope export beyond the Baltic States possibilities.
23. Conventional isotope production should be the focus of the manufacturing facilities, while the proposed accelerator facility should mainly be complimentary on

production on non-conventional radioisotopes, with possibility of limited production of common isotopes as fluorine-18 for particle therapy treatment planning necessities and treatment response assessment.

24. To boost the capacity and expertise in radioisotope production, involvement of Baltic scientific universities and research institutions in experiments as CERN MEDICIS and other European projects should be expanded;
25. The unique opportunity to use not just proton, but also helium-4 ion beams for radioisotope production in the proposed facility allows development of vast research programme possibilities in precision measurements of radioisotope characteristics, novel production method development, cross-sections measurements in nuclear physics and others [49].

V Education and capacity building

Development of such a large scale facility in the Baltic States, involving a lot of new specialties and scientific fields to the region as whole, indicates a clear need to understand pathways of ensuring education, development of human capacity and personnel training. This is one of the key considerations indicated both in bi-lateral meetings of 2022 [77] [78] [79] and also largely discussed in this workshop. To summarize on these aspects:

26. While the Baltic States currently has existing educational pathways and a reasonable number of staff practicing in radiotherapy, the expertise and training is in conventional radiation therapy – there exists a need for additional courses, exchanges to particle therapy centers and other activities to facilitate the personnel to gain necessary knowledge and skills specific to clinical particle therapy [62].
27. As was indicated by the opinion of specialists in *HITRIplus* project workshop later in 2023, such a re-specialization would require an exchange to particle therapy center for at least 6 months [65].
28. Different needs were identified both from clinical radiation oncology and medical physics perspective, which can be integrated in various stages of education – both at university curriculum, as well as further education course level [62].
29. Neccessity to develop clinical and scientific networks in the Baltic States related to the initiative was found to be crucial.
30. From the experience of European particle therapy centers, the aspect of personnel training and expertise building is one of keys for success of facility and considerations of such activities should be implemented at early stages of project development [66].
31. Experience from different European Commission funded projects [67] [68] [69] [70] oriented at capacity building in particle therapy were discussed, clearly indicating the need to consider creating a similar project proposal for the Baltic States in early stages of the initiative, with the focus on Marie Curie Initial Training Network programmes.
32. Number of educational resources and freely available courses exist already and would be highly beneficial for the community in the Baltic States;
33. A clear support for the project initiative has been shown by:
    - the ENLIGHT network [66], proposing to hold the next network annual meeting in the Baltic region with possibility of training course as part of the meeting;
    - the HITRI*plus* project [71], indicating a clear support for transnational access educational visits for the Baltic States medical community representatives to European particle therapy centers.

From the Baltic medical community representative side, a general support was shown in the meeting for further developments and investigations of the initiative. A clear need for work on possible large-scale **feasibility study** as well as for capacity building project proposals was indicated.

Workshop was also attended by representatives of inter-parliamentary Baltic Assembly as one of the key political stakeholders in project initiative. Baltic Assembly representatives indicated a clear support for the initiative as unifying, long-term project for the Baltic States and an opportunity that should not be missed. Proposal to jointly apply for European Union co-funding was made. Baltic Assembly representatives also indicated clear willingness to be involved in the project initiative from the political perspective, engaging with the parliaments and relevant ministries in each of the Baltic States.

Future steps of the initiative.

This dedicated workshop deliberated the following pertinent ideas for the consideration of the future work of CBG's „*Advanced Particle Therapy center for the Baltic States*" working group:

1) In order to proceed with this promising idea, a full-scale feasibility study of the project is needed. It shall assess feasibility of the facility of this research infrastructure from financial (business case), clinical (medical case), technological (technical outline, availability and R&D required) and multi-disciplinary scientific research perspective. In each of these segments, feasibility study would need to have involvement of experts from every Baltic State and CERN researchers, as well as representatives of European particle therapy centers. The best existing platform for such feasibility study is CERN based NIMMS collaboration.
2) As mentioned, NIMMS Technical Design Report is envisaged and could be available by the end of 2025. Involvement of Baltic researchers in development of this TDR is of utmost importance.
3) Serious consideration for joint actions or project proposal application (regional, EU or international) should be done aimed at capacity building of experts necessary for particle therapy facility. Such actions or project proposal might be done concurrently with the feasibility study.
4) It is important to support the educational visits of Baltic medical community representatives from radiation therapy departments – as teams of radiation oncologists and medical physicists – to European particle therapy centers. This would allow the exploration of the workflow and clinical needs of particle therapy, as well as could allow the first *hands-on* clinical experience with particle therapy. Such visits are possible within the opportunities provided by transnational access of HITRI*plus* project, representatives of which have indicated clear support for such Baltic community oriented visits. Visits are possible immediately based on the initiative of the clinical teams themselves.
5) Continued activities to raise awareness of the initiative in various communities relevant for the success of the project, such as patient organizations. Active full-spectrum stakeholder engagement is crucial for any further steps.
6) This report has to be submitted within CERN Baltic Group General Meeting, for consideration and potential approval.
7) Relevant parts of this report (constituting results of the Workshop) shall be submitted to the appropriate and specialized medical communities (e.g. conferences or journals) for peer-consideration and potential feedback.

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