Thunder Bay Regional Health Research Institute

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- uSv symbolizes microsievert – a unit of radiation dose that measures biological effects on human tissue. The worldwide average background dose for human beings subject to natural environments is 2400 uSv per year.
- The annual radiation dose limit to the general public of 1000 uSv is determined by the Canadian Nuclear Safety Commission (CNSC) and it is the same for both adults and children.
- We are exposed to various radiation levels when we undergo medical procedures. For example, an x-ray = 4 – 20 uSv (dental) to 700 uSv (pelvic); a CT scan = from 2.0 mSv (head) to 10.0 mSv (full body); a nuclear scan (i.e. PET) = 4.0 – 10 mSv; mammogram = 700 uSv. The actual amount for any test will vary depending on the size of the person and the level of detail required.
- In total eight cyclotrons of the size that TBRHRI is purchasing will be part of the proposed Canada-wide cyclotron network to produce Technetium-99m. (Tc-99m). Given our location in Ontario and the half-life of the products, we have deliberately selected a cyclotron size that is able to produce longer-life products, which can be shipped. This is the TR-24 purchased from Advanced Cyclotron Systems Inc. in Richmond, B.C. One isotope we hope to produce is Gallium-67 (Ga-67), which has a half-life of 3.3 days and is used to identify sources of infection. Already used at TBRHSC for the SPECT camera, its longer half-life makes Ga-67 an ideal isotope for distribution.
- A cyclotron is not being built in Chalk River as that facility uses a different type of production. As for the United States, they are also focussed on other technologies for production of Tc-99m.
- We are in the first stage of three stages of the CNSC licensing process and we hope to submit our licence to construct application in mid- to late August 2013. Any reports by the CNSC, as well as submitted applications, are available to the public through a Freedom of Information and Protection of Privacy Act (FIPPA) request.
- Once in operation, the cyclotron facility will run between 8 and 12 hours a day with one day a week reserved for routine maintenance. The facility will employ a minimum of 5 people at start-up to run the cyclotron facility – a Radiation Safety Officer (RSO) who is tested and approved by the CNSC for a Class II facility; a Cyclotron Technician; a Production Technician; a Quality Control Technician and a Facility Manager.
- The radioisotopes will be produced on an as-needed basis so no long-term storage will be required nor will large amounts be produced at one time. There will be processes in place for the handling of radioactive waste. For example, short-lived waste will be stored within the cyclotron vault until it has decayed to regular background levels of radiation. Long-lived waste will be stored in the vault and then disposed with the assistance of a licensed disposal company.
- Medical isotopes are currently transported to Thunder Bay on Air Canada passenger flights. Passengers would not likely be aware that this cargo was onboard. However, pilots would be made aware through required cargo manifests. If for any reason the pilot felt that the content of a package was suspicious, was a dangerous good that was not labeled correctly or was not listed properly on the manifest, he/she has the right to refuse transport of that package. Packages must be segregated during transport and during storage in transit from places occupied by persons to ensure that the dose by any one person does not exceed 1 mSv per year. (1mSv = 1000µSv)
- TBRHRI will be using licensed transporters such as FedEx to transport isotopes produced at the facility. Responsibility for the product is transferred to whoever is in possession of the product and each possessor must be licensed. Individual courier drivers do not have individual licenses - it is the courier company that holds the licence - however, the company is responsible for providing appropriate safety training to any employee transporting dangerous goods.

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- With respect to the danger of radiation exposure, the worst-case scenario would be if someone is in the cyclotron vault when it begins to operate. There are safeguards in place, however, including a last-person-out (LPO) button, which must be pressed before the cyclotron can operate.

- People who work in the hospital do not need to worry about radiation from the cyclotron. For example, someone working in the lab or office directly above the cyclotron will receive less than 50 uSv/year which is well below the annual dose limit of 1000 uSv/year. The Health Services Building in which the cyclotron will be housed is a distance of approximately 200 metres from the hospital.
- There is minimal danger during the transportation of the radioactive materials produced. During shipping, materials are packaged so the dose rate of the package is kept to a safe level and packages are designed to contain all radioactive material even if the inner container breaks.
- Packages have an inner container, a packaging layer (absorbent enough to soak up the contents of the inner container if broken) and a tough outer layer that will not collect or retain water. They will with-stand the effects of acceleration or vibration for routine transport conditions and can accommodate changes in ambient temperature or pressure. These containers undergo rigorous stress testing.
- A radioactive label is required on the inner container, as well as the outer package must have a radiation label affixed to it on both sides. The radioactive packaging and transport categories/labels are determined by the radionuclide, the activity and the form of the radioactive substance to be transported.
- The most common radiopharmaceutical that TBRHRI will be shipping is FDG, a sugar molecule that emits positrons. Cancer cells divide rapidly and take up sugar faster than healthy cells. Therefore, the FDG is taken up faster and the cancer cells 'glow' in the imaging.
- F-18 is incorporated into FDG used in PET CT imaging (Positron Emission Tomography). Tc-99m is a "go-to reagent" used for cardiology, bone scans, any SPECT imaging, etc. Ga-67 is used to detect the site of an infection. C-11 is a research isotope with a very short half-life which easily incorporates into drugs due to its carbon structure.
- FDG costs approximately $700 (shipping included) whereas the production cost is approximately $25 per dose.
- If transportation of an isotope is delayed, depending on its half-life, the product may become useless for its intended purpose. One reason TBRRI plans to produce isotopes with longer half-lives such as Tc-99m and Ga-67 is that it will allow for more time for delivery and we will be able to ship further distances to reach more people.
- When in operation the cyclotron and related equipment requires 175kW of electricity during operation. On its own, the cyclotron requires 85kW. There will be a dedicated line to run the cyclotron independent of the rest of the building and the machine will be operated mostly at off-peak times so the cyclotron activity should not affect the other tenants' power usage.
- For structural reasons and the sheer weight of the cyclotron machine (~22 tonnes), it will be located in the basement of the building at 1040 Oliver Road in a specially designed bunker. The bunker itself will consist of about 150 tonnes of lead, concrete and other protective materials.

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- There are several other cyclotrons in Canada of various sizes. They are located in Halifax, Ottawa, Hamilton, Winnipeg, Vancouver, Edmonton, Sherbrooke, and Toronto, and there is one planned for Saskatoon too. In total, including the proposed cyclotron in Thunder Bay, there will be 14 operating in Canada.
- These cyclotrons are manufactured by several different companies. The TR-24 Cyclotron that has been ordered for Thunder Bay is being manufactured by Advanced Cyclotron Systems, Inc. (ACSI) in Richmond, BC.
- Isotopes produced in Thunder Bay can be shipped, not just across Canada, but into the States and internationally depending on the half-life of the product and the proposed use of the isotope. In other words, export/import regulations change depending on whether the isotopes are for research only or intended for medical use.

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- Employment opportunities that will be available once the cyclotron is licensed for operation include radiation safety personnel, GMP drug manufacturing staff for synthesis and QA/QC, cyclotron operators and technicians (both electrical and mechanical), and researchers and their students. There will also be space in the lab to accommodate visiting researchers.
- Prior to using the facility, safety and procedural training will be required by anyone wishing to work there.
- Water and gases/air used in the facility are not released into the outside environment until after they have been drained into holding tanks, left to decay to background levels.

- Radiation is measured using dosimeters - thermal luminescent detectors that measure exposure of workers to ionizing radiation over time.
- When looking at equivalent doses it takes into account the difference in type of radiation. In other words, 1000µSv of gamma radiation = 1000µSv of beta radiation.
- There will be large quantities of lead in the shielding around the cyclotron facilities. To offset any potential health hazards, the labs will have hepa air filtration systems, and the cyclotron lab will have a separate air filtration system from the rest of the building.
- When in operation, there are magnetic fields released from the cyclotron. However, these will be contained within the bunker and will not affect medical equipment present in the lab on the floor above.

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- Having a cyclotron located in Thunder Bay has a distinct advantage over shipping in medical isotopes from Southern Ontario. Owing to the half-life of F-18 the hospital must purchase enough isotopes to image 32 patients; however, by the time the shipment arrives at the hospital, the isotopes have decayed significantly and can only supply enough for imaging 4 patients. Not only will this facility save the hospital money in the long run, it will allow TBRHSC to serve more patients, and there won't be the danger of losing shipments due to transportation delays or weather issues.
- Cyclotrons are becoming more common than nuclear reactors in Canada as they are safer to operate and do not have long-term environmental effects such as radioactive waste that takes hundreds of years to decay. The reactor in Chalk River is slated for shutdown in 2015 and the reactor in Pinawa, Manitoba is now being decommissioned.
- Students and faculty at Lakehead University and Confederation College will have the opportunity to use the facilities for research purposes and currently a process is being designed in order to facilitate this happening. The most important aspect of these collaborations will be to ensure that proper training will be completed prior to using the equipment. This will pertain to visiting researchers also.
- Although cancer is still prevalent in society, advances in diagnosis and treatments over the past 30 years would not have been possible without research accomplished with cyclotrons. The cyclotron and radiopharmacy will be available to researchers who are looking for new ways to diagnose the disease and to determine the best treatments.
- Workers in the cyclotron facility will be classified as Nuclear Energy Workers (NEWs) and will be allowed an quarterly radiation dosage of up to 3 mSv.
- CNSC radiation dose limits are measured every three months. However, the Thunder Bay facility will measure these more frequently during the first year of operations.
- It will be the responsibility of the Radiation Safety Officer (RSO) to measure all the tasks' levels of radiation in order to look at ways of reducing radiation if possible.
- Should CNSC regulations change over the years, the new standards will be assimilated into the licence requirements to ensure public safety.
- One microsievert (1 µSv) is equivalent to 0.1 millirem (0.1 mrem), an older measurement of ionizing radiation first used in the mid-1940s.
- For those people hired to work at the facility in the future, a certain skill set will be required but there will also be training provided for tasks specific to our facility.
- Although the cyclotron takes a tremendous amount of energy to operate (80,000 watts), it will operate the majority of time at night and will not affect the local hydro grid. The majority of runs will be midnight to 8:00am in order to have the isotopes ready for patients who are scheduled to have scans first thing in the morning.
- Initially the cyclotron will be running a couple of days per week but within a couple of years, we aim to be a 7-days-a-week operation.
- The cyclotron requires about 30-minutes to warm up prior to a production run.

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- The average dose of radiation has increased over the years as the population ages due to people wanting or requiring medical scans for diagnosis.
- The CNSC licence to operate is the same as a licence to produce isotopes. The licence to operate also gives the facility permission to distribute the materials produced.
- The radiopharmacy will be able to produce whatever dosage is required by a consumer. For example, TBRHSC's preference would be syringe doses to decrease exposure to their technologists.
- The capabilities of the MeV-24 Cyclotron will allow the facility to produce several different isotopes. Although currently there are no plans to produce Iodine-131 (I^{131} or radioiodine) which could be used to create high quality thyroid scans, there is a possibility to expand the cyclotron's capacity in the future.
- Currently, the radioisotopes that are planned for production are Copper-11 (C^{11}), Fluorine-18 (F^{18}), Technetium-99m (Tc^{99m}), Indium 111 (In^{111}), and Gallium-67 (Ga^{67}).
- For someone who can follow protocols exactly and is already trained in radiation safety, such as a medical radiation technologist (MRT), there will be opportunities for employment in the radiopharmacy.
- All staff hired to work in the radiopharmacy will be classified a Nuclear Energy Worker (NEW).
- It is possible that the radiopharmacy at TBRHSC could be moved into the radiopharmacy facility in the new building at 1040 Oliver Road as there will be enough space and the capabilities of the current radiopharmacy.
- Currently FDG is delivered through the Cancer Centre by a licensed courier trained for dangerous goods transport.
- The anticipated date of the first FDG dose to be delivered to TBRHSC is estimated at March 2015.
- Our facility will focus on supplying isotopes within Canada but marketing internationally is a future possibility.
- The cyclotron measures 1.5m^2, not including the beam lines, and weighs 25 tons.
- There is no time delay switching between making F^{18} and Tc^{99m} as both radioisotopes can be made simultaneously on different arms of the cyclotron.
- The synthesis unit used to make FDG actually sits inside a hot cell and is fully automated.
- Though the synthesis unit could be reprogrammed to synthesize new compounds, we will have a different machine specifically for production of research compounds.
- Quality control is not performed by the synthesis unit. Quality control will be performed separately by drawing off a sample from the vial, which will then be sent to Quality Control where it will be tested. Once the results are complete, Quality Control will notify the Shipping Department.
- The research production runs of isotopes will be conducted mostly during the day.
- Cyclotron technology has not changed substantially in the last 50 years other than it is a little more energy efficient and the magnets are a bit stronger.
- The difference between cyclotron magnets and MRI magnets is that the cyclotron has an electromagnet and the MRI has a superconducting magnet.

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- Although there will be a dedicated research lab at the cyclotron and radiopharmacy facility, the research labs at the Munro Street location will still be in operation.
- Although the CNSC requires us to have a decommissioning plan as part of our Licence to Construct, there is no exact date set for this process. The average life span of a cyclotron, however, is about 30 years.
- The installation of the cyclotron equipment requires workers specially licenced for the specific machine. Our cyclotron will be installed by the company that manufactured it – Advanced Cyclotron Systems, Inc. (ACSI) from Richmond, B.C.
- All staff will be monitored for radiation levels while working at the facility and the records of this data are kept for the life of the worker as they are attached to an individual's social insurance number and maintained by Health Canada. If the worker goes to another facility, the data collected at the Thunder Bay facility will be part of the worker's accumulative total. In the event that the worker's exposure goes above an acceptable level, an intervention will occur. In addition, ALARA is reviewed annually at a facility.
- Radioactive waste disposal will be handled by a licenced contractor. However, most radioactive waste will have decayed to background levels of radiation before being disposed.
- The cyclotron and radiopharmacy in Thunder Bay will produce enough isotopes to meet our local clinical and research needs and will be able to supply about 10 per cent of Canada's demand of Tc-99m (once running at full capacity).
- For future operations, we are able to double the capacity of the cyclotron as the bunker has been designed with expansion in mind. There is room to add an additional target beam as well as there is flexibility in the types of target materials that can be used. In addition, there is room in the lab to have additional hot cells installed at some point in the future.
- There will be about 6 dedicated staff on the clinical production side when operations begin but once operations are at 100%, it is hoped to expand to 18 employees on the production side over a couple of years. Staff on the research side will depend on the growth of the research program.
- Besides cancer, medical isotopes can be used in cardiac stress tests, in the diagnosis of bone disease and conditions of the central nervous system (such as imaging agents for the brain in cases of schizophrenia and depression) as well as be used for labeling white blood cells to help determine the site of an infection.
- Typically the Waste Gas Handling System (WGHS) will capture Carbon 11 (C-11), which has a half-life of only 20 minutes. The facility will not release any C-11 gas until after 10 half-lives have passed and the radiation levels have been tested. F-18 has a half-life of 110 minutes, for which we would wait 24 hours, test and then release when safe to do so.
- The hand foot monitors that staff and visitors use upon exiting the facility can scan for whichever isotope with which they may have come in contact that day. The person would choose the particular isotope option on the screen and then press 'start'.
- The facility can produce for research purposes now (since August 2015) but it will likely be about a year before we can produce for human consumption, as we will require Health Canada inspection and approval.
- We will be able to start the Health Canada process once our commissioning report to the CNSC is complete and we receive our Licence to Operate.

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- The expected life span of the facility is 30 years. The computers that control the cyclotron will likely become obsolete so as long as we can upgrade the system, the life of the facility will be lengthened as the actual cyclotron equipment has very few moving parts and should last much longer than 30 years.
- The TR24-Cyclotron is capable of making other isotopes than what we are currently planning to create so if something was to become obsolete there would still be opportunities to manufacture isotopes.
- Considering the periodic table, there are many possibilities for radioactive isotopes. Some possible isotopes would be Zr^{40}, Cu^{29}, Ga^{31}, In^{49} and Tc^{43}.
- On the research and development front, we are considering collaborations to work on using isotopes for sterility processes and to optimize mining processes.
- As of February 2016, the Cyclotron & Radiopharmacy has a Licence to Operate and is, therefore, able to produce radioisotopes for research purposes and for industry applications.
- Radioisotopes have been produced for TBRHSC to calibrate the PET equipment. Until the Cyclotron & Radiopharmacy receives Health Canada approval, however, no radioisotopes can be used for patients yet.
- Radioisotopes are not only used for cancer diagnosis and treatment but also for cardiac imaging, cerebral imaging, bone density measures and infection finding.
- MRI machines do not use radioactivity but radio waves and magnets instead. In a CT scan, however, X-ray tubes and detectors spin around the body taking multiple images. In this procedure a patient would receive about 4mSv of radiation.
- Our radiopharmaceuticals must be tested for sterility as this is a Health Canada requirement to ensure patients are not injected with contaminated product. Radiopharmaceuticals may become contaminated during the dispensing process if recommended procedures are not followed so a sample from every batch will always be Quality Control tested, including sterility testing.
- The FDG produced at the Cyclotron facility is in a sterile saline solution intended for injection into a patient's circulatory system (one we have received Health Canada licensing). This is a different method to treating a disease than the process of radiation therapy where the patient receives radiation from an external machine or from a brachytherapy seed implanted internally.
- If an employee reaches his or her radiation dose limits, that employee will be asked to work in an area that will not expose him/her to any further radiation.
- The magnetic field produced by the cyclotron is shielded by several feet of concrete around it, which protects the public from any electromagnetic hazards.
- In order for the Cyclotron facility to be able to provide FDG for patient use, we have to receive a Notice of Compliance as a result of an abbreviated New Drug Submission. (Application was submitted at the end of December 2016.)
- Production of radioisotopes on a cyclotron has much less environmental impact than production of radioisotopes on a nuclear reactor as the nuclear reactor's waste takes many years to decay. It is also safer to run a cyclotron versus a nuclear reactor. Cyclotrons can be turned on for production and then turned off when done, whereas a nuclear reactor must always be kept chilled to avoid equipment overheating and possibly causing a radioactivity leak.
- The Cyclotron Network across Canada consists of 4 larger cyclotrons (like Thunder Bay) and ten smaller cyclotrons. Thunder Bay's cyclotron has a higher energy (24MeV) so longer-lasting isotopes may be produced and shipped in the future.

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- Funding from FedNor, Northern Ontario Heritage Fund Corporation, the City of Thunder Bay, along with generous donations from private donors, has made this project possible. The business plan for the future includes revenue generation not just from sales to health facilities but also from providing radioisotopes for industrial applications in order to sustain operations at the facility.
- The Munro Street location, or ICR Discoveries building, now houses businesses as well as Research Labs. TBRHRI's Research Labs include some work that requires radiopharmaceuticals for imaging mice.
- Infection can be detected within the body by drawing a patient's blood, separating out the white blood cells, labeling the cells with a radioisotope and then injecting the white cells back into the patient. The labeled cells will migrate to the area of infection and the radioactivity can be imaged to indicate the location of the infection.
- After a patient has been injected with a radiopharmaceutical he or she must wait for it to be circulated through the blood stream. The scan is performed about 1 hour after injection.
- The radiopharmaceutical is eliminated from the body in urine. The urine is considered radioactive until enough half-lives have passed for it to decay to background levels so the patient is asked to flush several times to ensure there is nothing left in the bowl and the waste goes to a special holding tank.
- PET scans potentially offer better spatial/temporal resolution and overall image quality in comparison to SPECT, however, SPECT imaging is currently less expensive and there are more indications for SPECT covered by OHIP than there are for PET. Therefore, the plan is to produce both types of radiopharmaceuticals at the Cyclotron facility.
- The idea of shipping radioisotopes into Duluth is being investigated, taking into account that the nearest source of FGD is Minneapolis and our facility would have to receive FDA approvals to supply within the United States.

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