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Optimizing Performance and Safety for a Particle Therapy Accelerator

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Performance and safety are two key attributes of a medical device. Likewise in other sectors, the two attributes are generally inversely interdependent: the higher the performance, the lower the safety and vice versa. Because of that setting the two attributes is a matter of optimization. Performance and safety are analyzed and evaluated before the certification of the medical device respectively as benefits and risks. This is also performed for every design development by comparing the benefit-risk ratios, which must ideally increase or remain acceptable. This paper presents the methods for evaluating and optimizing benefits and risks that have been applied at MedAustron, including some results from selected performance increase projects.

Keywords: medical device, benefits-risks analysis, risk management, safety, benefit/risk ratio, optimization.

1. Introduction

Performance and safety are equally important for systems that operate in hazardous environments, such as nuclear power plants, chemical industries, transports and of course medical devices. For these systems, the performance is related to the benefits, which reflect societal and economic expectations. The ability to increase performance for higher benefits is limited by several factors: normative, technical, budget, and last but not least, by the risks that the community is willing to accept. In the EU, the market of medical devices is regulated by Medical Device Regulation MDR 2017/745. Performance and safety are defined in the annex II of the MDR, together with the general requirements that have to be implemented in the design of the medical device in order this is effective and safe.

This paper presents the experience with the optimization of performance and safety for the MedAustron Particle Therapy Accelerator (MAPTA). MAPTA is a particle accelerator which delivers proton and carbon ion beams for hadron therapy. MAPTA consists of particle sources, a linear accelerator (LINAC) and a synchrotron where particles are accelerated (up to 250 MeV p^+ and 400 MeV/u C^{6+}) and extracted toward the irradiation rooms. The beam reaches the positions and depth corresponding to the tumor volume, where the dose (Gray) is deposited as specified in the treatment plan. MAPTA started clinical operation in December 2016 after it received the certification as CE medical device. Since then, it has undergone several design changes, allowing new treatment indications, enhancement of single treatment effectiveness, and performance improvements.

The aim of this paper is to present the relationship between performance and safety in the feasibility study of a medical device and its performance driven developments. The starting point is the definition of performance and safety of MAPTA and the derived quantities benefits and risks. Performance of MAPTA is related to the quality of the delivered beam, which influences the effectiveness of a single patient treatment. Performance is also the duration of a single treatment session, which influences patient

comfort and the throughput (number of patients per year). For example, a shorter treatment session is more comfortable for the patient but it has also the benefit that the dose delivery becomes less prone to movement artefacts, therefore further increasing conformity to the treatment plan.

Safety of MAPTA depends on the ability to cope with failure scenarios by preventive and protective measures, eventually stopping the treatment in case of beam delivery errors. In the standard ISO 14971, safety is also defined by the absence of non-acceptable risks. Therefore, a medical device is safe if the risks are evaluated as acceptable during the intended use and foreseeable misuse.

Finally, in the same standard ISO 14971, benefits and risks are analyzed and compared. Risks are evaluated as acceptable when weighed against the benefits to the patient. The most innovative design solutions are the most promising for benefits, but often the most challenging for guaranteeing safety and reducing the risks. This is the point where trade-offs between benefits and risks are identified and the optimization comes into play. In this respect, the several years' experience with clinical operations makes MAPTA to be an appropriate example to show how to deal with the optimization of performance and safety through the evaluation of benefits and risks.

The paper consists of six sections. After the introduction, section 2 and 3 show the taxonomy of the benefits and risks respectively. Section 4 will include the foundation of the benefits and risks analysis. Section 5 includes the method to compare design alternatives, with respect to benefits and risks and other relevant quantities, which is exemplified for a few performance increase projects as presented in section 6. The conclusions are outlined in section 7.

2. Taxonomy of benefits

The design and development of a medical device aims at different benefits, which can be classified as it follows:

(i) To allow new treatment indications
(ii) To improve the effectiveness of the single treatment
(iii) To increase the throughput of the medical device.

To allow new treatment indications, means to upgrade the medical device in order to implement new protocols for a larger range of treatable diseases. For example, in a particle therapy accelerator, radiation heads with new treatment angles, new particle species as well as tracking devices for delivering the beam into moving organs, belong to this category. A new treatment indication brings benefits to a new cohort of patients. But, because all patient treatments "compete" for the same resource, namely the machine time of the particle therapy accelerator, the throughput of the other categories of patients potentially gets reduced. This is an **internal trade-off** problem for the user of the medical device, the solution of which would theoretically tend to the Pareto optimal solution.

To improve the effectiveness is related to the quality of the delivered treatment. For example, a higher accuracy of beam positioning improves the sparing of healthy tissue, and a constant beam flux increases the uniformity of the dose distribution in the treated area. The benefits are estimated for single patient treatment, the evaluation of which is for gain in scope of the user (e.g., the tumor control rate after 5 years).

To increase the patient throughput is related to the ability of the medical device to deliver the treatment in a shorter time. There are different means to improve the throughput for a particle therapy accelerator. One mean is by reducing the duration of the single treatment, for example by a faster dose delivery or by increasing the number of particles extracted during a single spill, thus reducing the number of needed cycles (fill-accelerate-extract) per treatment. Other means consist of optimizing the patient workflow, for example by shortening the switching time from an irradiation room to another. These performance increases bring benefits both to the single patient (a higher comfort is expected because of the shorter treatment session) and the patient population (a higher throughput is expected).

The increase of the patient throughput cannot be pursued without limits. For example, a shorter

patient treatment that is obtained by a faster dose delivery might affect beam stability, thus triggering safety interlocks more often and at detriment of operability of the medical device. This is an **internal trade-off** issue: the design upgrade that was intended to increase the throughput might eventually worsen the situation. Another trade-off exists and concern the beam quality. The beam commissioner must guarantee that beam quality is not adversely affected by the performance increase, and therefore that the effectiveness of the treatment remains the same. This is an **external trade-off** between the patient throughput and the effectiveness of the treatment.

3. Taxonomy of risks and safety implications

Every time a medical device is developed in response to a performance increase, it is mandatory to assess the implication with safety and risks, according to ISO 14971. The following points must be addressed:

(i) Higher existing risks because of increased likelihood or severity
(ii) New risks are introduced
(iii) Reduced effectiveness of existing risk control measures.

The first two bullet points are addressed by risk analysis, and the evaluation of the residual risk, which must remain within the acceptable limits. The third bullet point verifies that the risk control measures are still effective, which includes the compliancy with the functional safety standard for light ion beam particle therapy accelerators, IEC 60601-2-64.

The risk analysis for MAPTA estimates the risk by the Risk Priority Number **RPN**. The RPN is the pair probability **P** times severity **S**. P is the frequency of the hazardous situation and spans six categories from frequent to impossible. The severity S consists of five categories from negligible to life threatening. The fact that the risks are evaluated as acceptable is the necessary condition to approve the performance increase. Nonetheless the risk evaluation relies on a few assumptions that should never been underestimated. Besides the probabilistic nature of the risk analysis, the description of each failure scenario is characterized by uncertainty, called "epistemic uncertainty". In simple terms, the epistemic uncertainty reflects the knowledge of the system and consequently the completeness and accuracy of the failure scenarios that are identified and analyzed. Any risk analysis suffers from a degree of uncertainty. This is classified as "known unknowns" as long as the system analyst is aware about it, see Flage et al. (2015). The failure scenarios that fall in this particular category tend to have an unpredictable nature and they may lead to catastrophic consequences. It is difficult to identify their causes and describe the failure dynamics. There is a correlation between complexity of the system and the "known unknowns". This is also applicable to medical devices. Hence, the general recommendation to the manufacturer is to refrain from concurrently or simultaneously introducing upgrades into the same system as such to make the failure scenarios more interconnected and therefore complex to analyze.

4. Benefits and risks analysis

The benefits-risks analysis aims at evaluating whether a performance increase is acceptable. The metrics are the benefits and risks for the single patient and the patient population. The benefits and risks are inversely interdependent. A design improvement that leads to higher benefits is almost certainly associated with higher risks. And the opposite is also true; a safer medical device imposes stringent limits to the design development. Together with benefits and risks, the manufacturer shall consider the operability of the medical device which is related to its reliability and the up-time. The three quantities must be assessed in this order: the benefits first, followed by the risks and then operability. The project is approved if the evaluation of the benefits and the risks is acceptable and there is no significant impact on operability. Afterwards, operational data must be collected in order to verify whether the benefits meet the expectations, the risks confirm the initial estimates, and operability is not compromised, otherwise corrective actions must be taken.

The benefits and risks analysis (with the addition of operability) guides the choice among the design alternatives for the performance increase of a medical device. Because benefits and risks are interdependent and conflicting quantities, their optimization would converge to a Pareto optimal solution, under constraints that reflect the respective acceptability criteria. The problem setup

is exemplified in the benefit and risk diagram in Fig. 1. The medical device is represented with the pair (x, y), which accounts for the initial risk and the initial benefit respectively. The acceptable region, shown in green, is delimited by the benefit and risk thresholds. The region out of the respective benefits and risks thresholds is non-acceptable and the project is rejected. This is not always the case if the medical device falls in the other two regions in which the benefits or the risks are non-acceptable. For example, experimental therapies can be authorized for certain patients if high benefits justify much higher risks.

The rate between the initial benefit and risk is the **benefit-risk ratio**, represented by the slope of the dashed straight line. The performance increase leads to the medical device leaving the coordinate (x, y), and moving towards the direction of the expected benefits increase. At a certain point, the risks are affected as well. The relative benefit-risk ratio is the ratio between the relative benefit increase and the relative risk increase. The ideal situation is when the relative benefit-risk ratio does not decrease and possibly even increases with respect to the initial benefit-risk ratio, see trend (1) in Fig. 1. If it decreases like in trend (2), then this is also fine provided that the benefit keeps increasing and the risk remains acceptable. The operability of the medical device can be added as the third dimension in Fig. 1 (the z axis) to compare design alternatives that have a similar benefit-risk ratio.

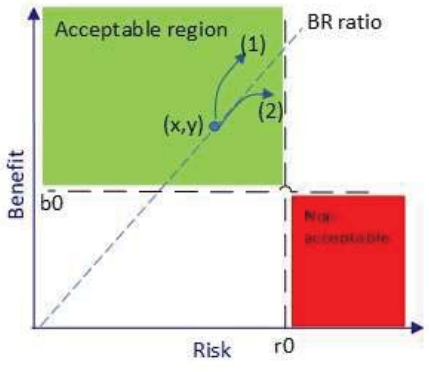

Fig. 1. Benefit and risk diagram.

The diagram in Fig. 1 offers an intuitive method, with some drawback due to its qualitative nature. The most relevant drawback is that the two (three) quantities are not homogeneous. Nonetheless, there exists a transformation of the benefits as potential risk reduction for the patient (the medical risk), which was first introduced in Filippini (2022). After the transformation, the optimization can be performed on the homogenous quantities medical risk (as counterpart of the patient benefit) and technological risk, which allows the quantitative evaluation of the benefit-risk ratio.

5. Analysis of design alternatives

This section provides a method for the qualitative analysis of design alternatives for a medical device based on benefits, risks and operability issues plus engineering costs. The method is exemplified for three categories of performance increase projects for a particle therapy accelerator. The three categories are 1) intensity of the particle flux, 2) effectiveness of beam extraction and 3) patient treatment workflow. They are chosen because they cover the medical device from different points of view both of the manufacturer and the medical user. These three categories provide increased performance of the facility for clinical use. Moreover, they reflect performance aspects that are in a tradeoff relationship with safety when changes are made.

5.1 Intensity of particle flux

The project consists of increasing the beam intensity (particles/sec), for example by reducing the extraction time and/or increasing the number of particles extracted per spill that reach the target tumor (see also 5.2). The time needed to deliver the dose into the single spot is reduced, and as a consequence the treatment time gets shortened.

Benefits: the reduction of the treatment time augments the patient comfort in addition to the increase of the patient throughput for all patient categories.

Risks: no new risks are introduced, but the effectiveness of the safety functions to protect the patient in case of beam delivery errors is certainly affected. As a consequence, an increase of the residual risk is expected, which is proportional to the increase of the particle flux rate.

Operability: there are no significant operability issues with this performance increase.

Costs: the engineering costs shall consider the retuning of the first stages of the accelerator to generate more particles, e.g., by reconfiguring software and firmware. The costs are relatively modest.

5.2 Effectiveness of the beam extraction

The project consists of increasing the number of particles extracted per cycle, for example by using new beam extraction methods that can exploit a larger fraction of beam out of a single spill. The number of cycles per treatment is reduced and as a consequence the treatment time gets shortened.

Benefits: similar to the higher particle flux. In addition, depending on the new extraction method, the quality of the extracted beam can be improved for example by reducing the intensity fluctuations.

Risks: new risks are introduced because of the new extraction method. Similar to the higher particle flux, the effectiveness of the safety functions in case of beam errors might be affected as well.

Operability: there are no operability issues with this performance increase. Conversely, the reduction of the cycles might have positive effects on the reliability of those accelerator components the life time of which depends on the number of cycles.

Costs: because of the development of new accelerator components, the engineering costs are the highest in comparison with the other performance increase projects.

5.3 Optimization of the workflow

The project consists of reducing the time intervals among the events that trigger the command of the accelerator components during the execution of cycles (fill, accelerate and extract).

Benefits: similar and possibly higher than the other performance increase projects.

Risks: the optimization might set too tight margins between two consecutive time events, such that some of the existing failure scenarios become more likely to happen, eventually increasing the risk for the patient.

Operability: because of the reduction of the time intervals between timing events, more patients can be treated and therefore more cycles per day are executed. As a consequence, the lifetime of all those components that are cycle dependent will be shortened, ending up with an increase of the failure rates on a long run.

Costs: the project consists of redefining the timing sequences. It is basically a software upgrade, with relatively modest costs.

Table 1. Comparison of performance increase projects. ("+" means increase and "-" means decrease of the respective quantity).

	Higher Part. flux	Effective Extraction	Optimized Workflow
Benefits	+	+	++
Risks	++	+	=/+
Operability	=	+	-
Costs	+	++	=
BR ratio	(-/=)	(=)	(+)

The results of the comparative analysis of the three projects are shown in the Table 1. Each quantity is qualitatively assessed in terms of the expected improvement trend with "+" (or "++") with respect to the initial performance. Similarly, symbol "-" means a decrease of the quantity after the change is made, and "=" means that there is no significant change. The three symbols "+", "-", "="shall be used together with the diagram in Fig. 1, in scope of a decision-making process and the assessment of the benefit-risk ratio. For example, the increase of the higher particle flux ends up with risks that are potentially higher than benefits, which eventually results into a decrease of the benefit-risk ratio, here represented by "-/=". On the contrary the optimized workflow has higher benefits in comparison with the risks, therefore the benefit-risk ratio is expected to increase "+".

The highest benefits are reached by the workflow optimization project, which has the highest benefit-risk ratio. The increase of the particle flux has the

highest potential risks, and the lowest benefit-risk ratio. The most balanced project is the increase of the effectiveness of the extraction method. Nonetheless, this project has the highest engineering costs.

6. Examples

This section analyzes five performance increase projects of MAPTA that have been implemented from 2017 to 2023. The projects are assigned the names used during their realization. They are:

Performance Increase Project 1a (PIP1a): was a workflow optimization project for protons. It allows to artificially shorten the accelerator cycle length if no further particles are needed for a given energy slice, thereby reducing the irradiation time.

Performance Increase Project 1b (PIP1b): was a project to increase the particle flux for protons by a factor of 2.5 and the available number of particles per cycle by a factor of 5. It was accompanied by the introduction of RF channeling to reduce the intensity fluctuations.

Cycle Skimming (CySk): was a workflow optimization project for protons and carbon ions. It reduced the overall cycle time by optimizing and parallelizing several processes, e.g., the injection, beam preparation at flattop and beam extraction.

Performance Increase Carbon (PICar): was the equivalent of PIP1b for carbon ions. The flux was increased by a factor of 1.75 and the available number of particles per cycle by a factor of 4.

Magnetization Time Reduction (MTR): was a workflow optimization project for protons and carbon ions. It reduced the times needed for magnet conditioning when switching to other irradiation heads between the treatments of different patients.

The benefits and risks of the five projects are analyzed with respect to four representative targets, two treated with protons and two with carbon ions.

- Proton head adenoma (small target)
- Proton prostate carzinoma (large target)
- Carbon H&N carzinoma (small target)
- Carbon pelvis pathy (large target)

The results are collected as actual benefits and average RPN. The benefits reflect the reduction of occupational time per single treatment. These are simulations and they are in excellent agreement with the operational data. This figure is directly related to the number of patients that can be treated per day, therefore the patient throughput. The average RPN shows the % of overall risk increase caused by the project. The average RPN is calculated over the total individual risks that have been estimated and mitigated for single patient treatment session. In a few cases, the project does not introduce new risks, which is the case for PIP1a and MTR, both being workflow optimization projects.

The results are shown in Fig. 2 and Fig. 3 for proton targets and carbon ions targets respectively. The occupational times are normalized, so to calculated the % time reduction of each project starting from the initial conditions of MAPTA. Analogously the RPN refers to the % of increase with respect to the initial conditions.

Table 2 compares the five projects with respect to the benefits, risks, operability and engineering costs. Like in Table 1, each quantity is given the expected trend: positive with different degrees (=/+, +, ++), neutral (=) or negative (-/=, -). For the engineering cost only (+) and (=) trends make sense, where (+) means that the project is demanding in terms of time and resources. The performance increase projects PIP1a, PIP1b and CySk bring the highest benefits. CySk affects all types of treatment indications, but it introduces the highest risks. PICar brings benefits for carbon ion treatment indications with a risk increase that is higher than the other projects. There are no significant operability issues with the five projects. In term of engineering costs, the PIP1b project has been the most demanding one.

Table 2. Comparison of five performance increase projects implemented in MAPTA.

	PIP1a	PIP1b	CySk	PICar	MTR
Benefit	++	++	++	+	+
Risks	=	+	+	++	=
Op	=	=/+	=/-	=/+	=/-
Costs	+	++	+	+	=/+
BR Ratio	(++)	(+)	(+)	(=/+)	(+)

In conclusion, all performance increase projects have a positive BR ratio, like the type (1) behavior of Fig. 1. PIP1a is the one with the highest BR ratio (++). This is because it was the first performance increase project, and it exploited the largest margin of improvement. The later projects bring less benefits than the earlier ones, with the margins of improvement being tighter and more challenging to meet.

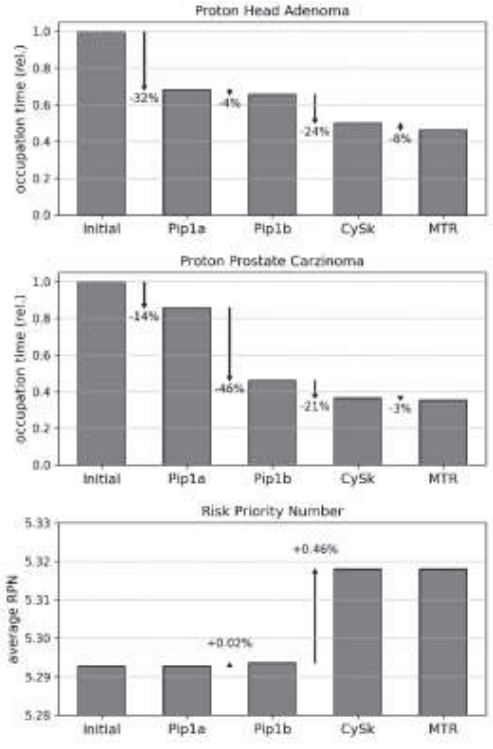

Fig. 2. Comparative benefits and risks analysis for two exemplary proton targets.

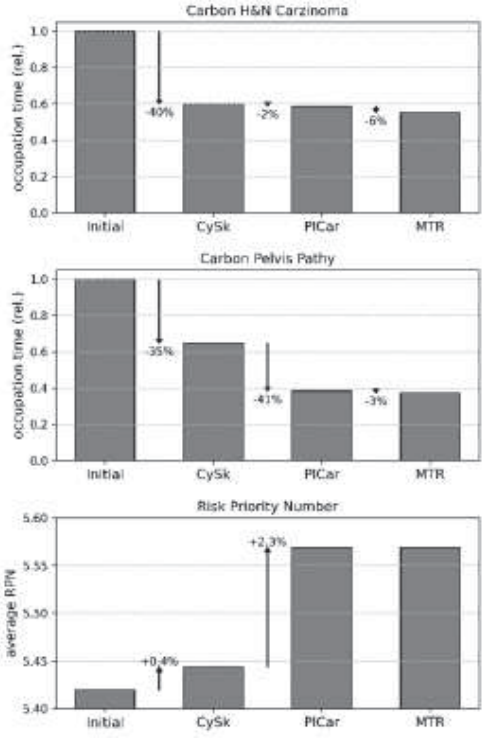

Fig. 3. Comparative benefits and risks analysis for two exemplary carbon ion targets.

7. Conclusions

The field of medical devices is driven by innovations in engineering, medicine and biology, with the objective to improve effectiveness and performance for clinical purposes. This improvement process must comply with the Medical Device Regulation MDR 2017/745, which authorizes the use of a medical device only if this is effective and safe, namely "the risks weighed against the benefits for the patient are evaluated as acceptable".

This paper has shown the experience with the optimization of performance and safety (and the derived quantities benefits and risks) of the MedAustron particle therapy accelerator MAPTA. MAPTA started clinical operation in 2016 and since then has undergone several design developments, as performance increase projects. A few of the most significant performance increase projects have been analyzed with respect to benefits and risks, and their benefit-risk ratio.

The analysis has also considered the impact of the project changes on operability of the medical device as well as the costs for the realization. The operability is especially critical for a particle therapy facility to allow the execution of the planned treatments without disruptions. Engineering costs help to decide among design alternatives if they show similar benefit-risk ratio.

MAPTA is under continuous design improvement and more challenging projects exist to further enhance its performance. For example, multi-energy extraction and dynamic intensity control will allow to further reduce the treatment time while keeping the same dose deposition accuracy. Emerging treatment modalities, such as FLASH therapy, show very promising increases in treatment efficacy while simultaneously drastically reducing the treatment time. MAPTA is already FLASH capable, from a technological point of view. Nonetheless, FLASH will require challenging safety strategies, with due consideration of the risk environment required.

8. Acknowledgments

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