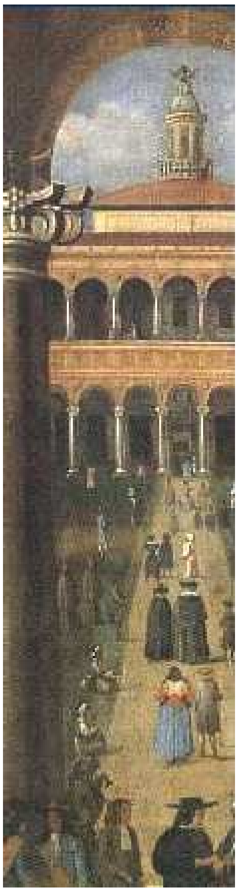

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THE SOCIO-ECONOMIC IMPACT OF THE NATIONAL HADRONTHERAPY CENTRE FOR CANCER TREATMENT (CNAO): APPLYING A CBA ANALYTICAL FRAMEWORK

CHIARA PANCOTTI GIUSEPPE BATTISTONI MARIO GENCO
MARIA VITTORIA LIVRAGA PAOLA MELLA SANDRO ROSSI
SILVIA VIGNETTI

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Via Conservatorio 7
20122 Milano
tel. ++39 02 503 21501 (21522) - fax ++39 02 503 21450 (21505)
http://www.economia.unimi.it
E Mail: dipeco@unimi.it

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The socio-economic impact of the National Hadrontherapy Centre for Cancer Treatment (CNAO): applying a CBA analytical framework

Chiara Pancotti*, Giuseppe Battistoni**, Mario Genco*, Maria Vittoria Livraga***, Paola Mella***, Sandro Rossi*** and Silvia Vignetti*

* CSIL, Centre for Industrial Studies

** Istituto Nazionale di Fisica Nucleare (National Institute of Nuclear Physics)

*** National Hadrontherapy Centre for Cancer Treatment (CNAO)

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Abstract

This paper provides an assessment of the net welfare impact of the National Hadrontherapy Centre for Cancer Treatment (CNAO) located in Pavia (Italy) in a thirty year-time period. CNAO is an applied research facility specialised in hadrontherapy, an advanced oncological treatment showing clinical advantages as compared to traditional radiotherapy, at the same time being more expensive as it exploits accelerators technology and sophisticated control and dose delivery systems. The methodology used to assess costs and benefits draws from the standard cost-benefit analysis (CBA) adapted in an innovative framework developed to account for the specificities of research infrastructures and complemented by risk analysis. The analysis shows that with a fairly high probability the Centre provides a net contribution to society's welfare. Source of benefits are mainly health treatments to patients, for whom gains in terms of longer or better lives are guaranteed as compared to a counterfactual situation where they are treated with conventional therapies. Such benefits are the direct consequences of the application to end users of the knowledge developed in the Centre with research activities and are quantified and assessed on the basis of conventional economic evaluation approaches for health benefits. Additional benefits generated by the Centre are typical of research infrastructures in different scientific domains and refer to technological spillovers (namely creation of spin-offs, technological transfer to companies in the supply chain and to other similar facilities), knowledge creation (production of scientific outputs), human capital formation (training of doctoral students, technicians and professionals in the field of hadrontherapy) and cultural outreach (students, researchers and wider public visiting the facilities). This test shows that a CBA framework for assessing the impact of a particle accelerator specifically designed to provide medical treatment is a promising avenue as compared to existing alternative methodologies informing decision-making. Further research is however needed to fine tune the methodology, in particular for what concerns technological spillovers and knowledge creation benefits.

Keywords: Cost-benefit analysis, Research infrastructures, Healthcare, Hadrontherapy

JEL Codes: D61, D81, I23, O32

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1 Introduction

Facilities for applied research are infrastructures delivering technologically advanced services to users (scientists, citizens or firms) involving practical application of science. Differently from fundamental research, in applied research facilities the scientific knowledge developed in given communities is exploited to respond to a well-identified need of specific category(ies) of users. Still, the experimental nature of the activities performed requires continuous investigation to adjust, fine tune and adapt theories, methodologies and techniques for continuous knowledge advancement, typical of science research. They also require large and expensive high-tech equipment and professional expertise.

A privileged field of application of scientific knowledge is health-care, here new technologies to implement experimental treatments are constantly being developed. Experimental novelties are often associated with higher costs than existing and more conventional treatments, thus the need to compare the new developed treatments to the existing ones on the basis of economic and welfare considerations arises. In particular, hadrontherapy is a field where knowledge and technologies developed by the particle physics scientific community is used for delivering oncological treatments.

Hadrontherapy is a kind of high-precision radiotherapy that employs subatomic particles called hadrons. Although, strictly speaking, the term "hadrons" can also refer to neutrons, it has become common to restrict the name hadrontherapy to treatments that employ positively charged particles, such as protons, helium ions, carbon ions, neon ions and oxygen ions. Hadrontherapy was proposed for the first time by the nuclear physicist Robert Wilson in 1946[1] and the first patient was treated at the Lawrence Berkeley Laboratories, California, in 1954. The pioneering age of hadrontherapy was up to the 90's: treatments were initially carried out in nuclear physics research centers and could rarely rely on adequate imaging, treatment planning, or patient setup technologies. Initially, the clinical applications were limited to few parts of the body, as accelerators were not powerful enough to allow protons to penetrate deep in the tissues. In the late 1970s, improvements in accelerator technology, coupled with advances in medical imaging and computing, made proton therapy a viable option for routine medical applications. One of the most relevant experiences began in 1973 at the Massachusetts General Hospital in cooperation with the Harvard Cyclotron Laboratories and employed proton beams. Results obtained in this first phase prompted the construction in 1992 of the first hospital-based proton therapy facility in Loma Linda, California. Treatments with different species of ions (helium, neon and others) were initially performed at the Bevalac Laboratories of the University of California, at Berkeley in California, but were not subsequently pursued in the USA. The Heavy Ion Medical Accelerator in Chiba (HIMAC) was the first hospital-based facility to employ ions, and it began operation in 1994 in Japan. HIMAC selected carbon ions as the most promising particles. Carbon ions have been employed in another hospital-based Japanese center (Hyogo Ion Beam Medical Center, Hyogo). Since 2010 Heildelberg facility is treating patients both with protons and carbon ions, and since 2011 CNAO facility too. Actually in Austria the MedAustron Center is in the commissioning phase and the first patient is foreseen for end of 2015. Nowadays, protons are used in 45 facilities, but also the use of Carbon ions is more and more wide spread. The number of dedicated hadrontherapy centers is now rapidly increasing.

As of today, hadronterapy is a very promising technology for cancer treatment, at the same time it is expensive and requires highly trained personnel as well as large facilities. This calls for a serious examination about whether it is worth to spend considerable amounts of public money in financing it and, if so, how social benefits can be maximised.

In principle, when a decision about investment priorities needs to be taken, costs of any project have to be assessed against the associated social benefits in order to check whether the latter exceed the former. However, as discussed in Pellegrin, Pancotti and Vignetti (2014), when the investment project entails the construction of a research infrastructure (RI) the assessment is often based, at best, on a combination of a scientific and business case, and, in the worst case, on the bargaining interplay of

[1] Wilson, R.R. (1946) 'Radiological use of fast protons', *Radiology*, vol. 47, pp. 487–491.

scientists, decision makers, business actors and the other stakeholders with an interest in the project implementation. In the field of experimental health treatment the assessment is complicated by the shortage of clinical evidence. Overall, a lack of an economic evaluation framework results in the absence of welfare considerations within the decision making process.

Cost-Benefit Analysis (CBA) is a recognised evaluation technique adopted by international institutions and governments in public decision-making to assess the socio-economic profitability of investment projects in many fields. In particular, there is a long worldwide experience in the social cost-benefit analysis of infrastructures in transport, energy or environment, and more recently health, education, culture and other fields. Under CBA, the costs and benefits associated with an investment project over a given long-run timeframe are expressed in monetary units, and the sign of the net benefit is used as the decision criterion. Prices adopted to value costs and benefits are however not those observed on the market but accounting prices expressing the social opportunity costs of the project's inputs and outputs. The key strength of CBA is that it produces information of the project's net contribution to the society welfare, synthesised into simple indicators, such as the Net Present Value (NPV) and the Internal Rate of Return (IRR). This leads to the possibility to compare several investment options.

The most challenging task of CBA consists in attaching a monetary value to non-market benefits. In the fields where CBA has a long-lasting experience, a set of theories and methodologies for their estimation is available and well established (see e.g. Drèze and Stern 1987, Florio 2014, Johannson 1991, Pearce *et al.* 2006). Even in the healthcare sector, where the difficulty of measuring health and life saved in monetary terms is a controversial issue for the ethical problems that arise, the CBA theory is well established and quite often used (see for instance Landefeld and Seskin, 1982, Johannesson and Jönsson, 1991, Sund, 2010). The same does not apply for research infrastructure, whether they are pure or applied ones. In this field some preliminary attempts to provide guidelines for consultants and public officers involved in appraising research infrastructure projects have been made.[2] Similarly, some empirical attempts to measure the economic return of investment in research and development sector exist.[3] However, it is recognised that the application of the CBA framework in this field is limited.

This paper illustrates how a CBA model based on a sound theoretical framework, as that developed in Florio and Sirtori (2014), can be empirically used to assess the economic and welfare impact of a particle accelerator specifically designed to provide medical treatment and to carry out research. Specifically, the paper aims at illustrating how the mentioned CBA theoretical model can be applied to a research facility in the medical field, i.e. the National Hadrontherapy Centre for Cancer Treatment in Pavia (IT). While the paper focuses on the analysis of a specific infrastructure, it more generally provides useful insights for the economic assessment of applied research infrastructure.

The structure of the paper is the following: In *Section two* we provide a brief presentation of the CNAO infrastructure, highlighting its research nature and presenting its costs. In *Section three*, we provide a brief restatement of the conceptual CBA model for research infrastructures. From *Section four* to *Section Nine* we discuss the benefits associated to CNAO. In particular, applied research benefits on patients, use of experimental beam line to third parties, knowledge outputs, technological externalities, human capital development, and wider cultural effects are presented. For each of these six effects we mention empirical approaches for estimation of marginal social values. *Section ten* concludes by putting together the cost and the benefit sides of the discussion and presents the CNAO expected net present value.

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[2] In 2009 the Czech government, in collaboration with the JASPERS team of the European Investment Bank, developed a working document providing guidance on the methodology to compute the CBA economic indicators for projects in this area. A revised and extended staff working papers has then been drafted by JASPERS (2013). Further, the European Commission (2014) provides some indications to estimate the economic return of public investment in the research, development and innovation sector.

[3] See Del Bo, 2014 and Pancotti et al. 2014 for an overview of the literature.

1 The research facility

1.1 What is Hadrontherapy

Radiotherapy is the medical application of ionizing radiation to treat cancer. In conventional radiotherapy, beams of Gamma-rays or of X-rays (high energy photons) are produced by radioactive isotopes or by accelerated electrons and then delivered to the patient to destroy tumor cells. When the irradiating beams are made of charged, fast non-elementary particles made of quarks (called "hadrons") such as protons, neutrons and light nuclei, the word "hadrontherapy" is used to describe this peculiar kind of oncological radiotherapy.

As compared to conventional treatment hadrontherapy shows a number of clinical advantages in terms of increasing the possible survival rate of patients and reducing side effects. This is due to the inherent physical and radiobiological properties of hadrons whose in depth understanding is due mainly to the complex experiments of particle physics.Unlike X-rays, the hadron beams deposit almost all of their energy in a sharp peak – the Bragg peak – at the very end of their path. This makes it possible to target a well-defined cancerous region at a depth in the body with reduced damage to the surrounding healthy tissues (see Fokas *et al.*, 2009; Loeffler and Durante, 2013; Tsujii *et al.*, 2014). In addition, the beams can be scanned and using variable penetration depths any part of the tumour mass can be accurately and rapidly irradiated. Finally, while the advantages of protons over photons are quantitative in terms of the amount and distribution of the delivered dose, there is evidence that carbon ions show an increased radiobiological effectiveness at the end of their range that allows the treatment of radio-resistant tumours such as those of the brain, lung and liver.

Such clinical advantages are associated to higher economic costs of the therapy. It is estimated that while the conventional therapy costs approximately EUR 6,000 per patient, hadrontherapy costs approximately EUR 20,000. Therefore, hadron therapy now faces the challenge of delivering a cost-effective, high-precision cancer treatment. In order to maximize cost-effectiveness, an accurate selection of the most suitable patient is carried out in order to provide the therapy on those patients where the net clinical benefit are maximised as compared to the conventional therapy. As a result, hadrontherapy is not a replacement for conventional radiotherapy or surgery, but it is a better treatment for those tumours that are located close to vital organs that would be unacceptably damaged by Gamma- or X-rays, or in pediatric oncology, where quality of life, late side effects and the risk of secondary tumors are a major concern (MacDonald *et al.*, 2012).

The high costs associated with hadrontherapy are mainly due to the fact that it needs significant capital investments for equipment such as accelerators, beamlines and gantries as well as buildings hosting the facilities. For this reason for nearly 20 years, it was based exclusively on accelerator facilities developed for nuclear physics. Only at the beginning of the Nineties the first proton accelerators started to be constructed in hospital-based clinical centres. Since the establishment of the first hadrontherapy facility, around 110,000 patients worldwide have been treated with protons. Conversely, only around 15,000 patients have been treated with heavier ions, generally carbon (NuPECC, 2013). Proton therapy compared to carbon ion therapy is in fact much more developed and in a sense much more conventional. As such, a proton therapy market has developed and these accelerators can be purchased on the market[4]. On the contrary, synchrotrons needed for carbon ion therapy are usually tailored and built in-house by research teams composed by high energy physicists, accelerator experts, radiobiologists. They are usually the result of large research collaborations.

Although Bragg Peak properties were known and exploited since 1950s, hadrontherapy early treatments were carried out, as a secondary activity, in research centres equipped with particle accelerators used for fundamental research in 1990s. Hadrontherapy is still in development, much more than other radiotherapy approaches, receiving important contributions from multidisciplinary scientific research including, accelerator physics, medical physics and biology. Its development is

[4] Supplying companies are for instance IBA, Varian, Mitsubishi and Hitachi.

strictly linked with improvements in the field of technological research, such as imaging systems for tumours localization and contouring. Great part of this research activity is carried out in the hadrontherapy centres, or in direct collaboration with them.

Despite the long time since hadrontherapy is in use, the limited number of such therapy centers in the world is responsible, in part, of the small number of treated patients (15,000 patients treated with Carbon ions, 110,000 the ones treated with protons). Furthermore, the clinical practice is limited as well, especially in carbon ion therapy, and the actual protocols are still based on clinical research. For this reason, most hadrontherapy institutions, and CNAO is one of them, are clinical and research centres at the same time.
CNAO activities are based on the previous clinical experience and results of similar centres; moreover, research activities are ongoing and are foreseen for the future, in order to provide the requested evidence and to maximize the probability that the knowledge so acquired will be able to modify clinical practice.

1.2 Project idea and construction of CNAO

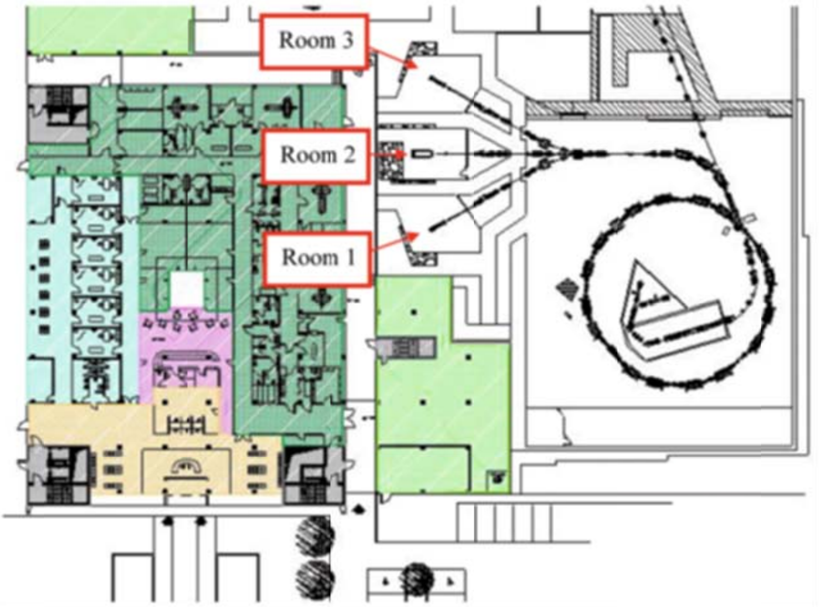
The construction of CNAO infrastructure began in the summer of 2005 and lasted until 2010. However, the original project idea can be dated back to 1991 when a report entitled "For a Centre of Teletherapy with hadrons" by Ugo Amaldi[5] and Giampiero Tosi was published. This report aroused the interest of Nicola Cabibbo, then President of the Italian Institute for Nuclear Physics (Istituto Nazionale di Fisica Nucleare - INFN), and in 1992 initial funding was provided for a study, called ATER, of a new accelerator that could accelerate both protons and light ions for use in the treatment of deep tumors. In 1995, Amaldi convinced the CERN's Director of the opportunity to design, at European level, a synchrotron optimized for therapy. This design study called Proton Ion Medical Machine Study (PIMMS) took place from 1995 to 2000 and involved researchers from CERN, TERA Foundation[6], GSI[7], Oncology 2000[8] and MedAustron[9]. In the years 1998-2003, TERA Foundation drew from the mentioned study a more compact version of the accelerator called the PIMMS/TERA, which later evolved into the version of CNAO realised in Pavia (Italy) and managed by the CNAO Foundation, a private law entity composed by different members[10].

The CNAO infrastructure comprises two broad distinct areas: the high technology components, made of a set of accelerators and transport lines of particle beams, and a clinical 'day hospital' facility, comprising reception desks, waiting and changing rooms. The two areas are combined in the treatment rooms, where the beam lines generated in the facility are used to deliver the therapy. The heart of the Centre is the hall containing the accelerators and the beam lines. The main accelerator is a synchrotron, a circular ring of about 25m in diameter able to accelerate proton and ions to a maximum

[5]Professor Ugo Amaldi is one of the most distinguished physicists in the area of particle accelerators. He became the spokesman of the Delphi experiment at CERN's LEP electron-positron collider in the 1981. Within a broad spectrum of research interests, he dedicated in particular to the promotion of hadron therapy based on novel accelerator concepts designed for medical application. In 1992 he founded the TERA Foundation working on the design of treatment centres.
[6]The TERA Foundation is a non-for-profit moral entity created in September 1992 and which has been officially recognized by a Health Ministry decree in 1994. The main aim of the TERA is the development, in Italy and abroad, of the hadrontherapy tecniques. In order to realise its aim, TERA has promoted the Hadrontherapy Programme, with over 200 physicists, engineers and informatics experts participating in its multiple projects. The construction of CNAO stems from this Programme (see Amaldi and Magrin eds.).
[7]The Oncological Clinic of the University of Heidelberg and the Deutsches Krebforschung zentrum (DKFZ).
[8]A research centre from Czech Republic.
[9]A research team at Wiener Neurstadt in the South of Austria, which later realised the Med-Austron centre, an ion-therapy and research centre with a synchrotron accelerator complex based on the CERN Proton Ion Medical Machine Study (PIMMS) and its further development and technical implementation by the Italian CNAO Foundation.
[10] The founding members of CNAO are: the Ospedale Maggiore Policlinico Mangiagalli e Regina Elena (Milan), the Policlinico San Matteo (Pavia), the Istituto Nazionale dei Tumori (Milan), the Istituto NeurologicoBesta (Milan), the Istituto Europeo di Oncologia (Milan) and the Fondazione TERA (Novara).The founders were joined by additional institutional partners: INFN, University of Pavia, University of Milan, Milan Polytechnic, the Municipality of Pavia and the Cariplo Foundation.

energy of 400 MeV/u[11] (corresponding to 27 cm penetration depth in water). The synchrotron is composed by the vacuum line, the RF cavity, 16 dipoles and 24 quadruples. Inside the ring the source, the lines of injection and the linear accelerator, are placed. Outside the ring there are four extraction lines (three horizontal and one vertical) leading the extracted beam into three treatment rooms where it is possible to perform both proton and carbon ion therapy (Rossi, 2011).

Figure 1 Map of the Centre



Source: CNAO

The facility relies on an active dose-delivery system, meaning that scanning beams are used in the Centre. The scanning system allows "painting" the dose within the tumour volume, a system which distinguishes the CNAO facility from others and has been developed by TERA. This technique results in a significant improvement of the conformity of the dose distribution within the target volume and thus is expected to improve the treatment outcome.

An experimental beam line with a dedicated room for research activities was also part of the initial project design. While the latter was built during the construction phase, the research line has not been realised yet. At present, the three existing beam lines can be used for research activities only when treatments or other activities related to the treatments or the management of the services are not carried out (for example partially during weekends). Delivering another beam line fully dedicated to research activities from insider and outsider researchers is therefore a necessary step to optimise the management of the Centre and enhance its potential as research infrastructure. Potential users of the research line are expected to be not only the scientific community but also the industry which could be charged for the use of the infrastructure.

At the beginning of 2014 CNAO in collaboration with INFN received funding for this upgrade. The construction has started in summer 2014 and will last until the end of 2017. The planning and construction of the research line has been realized by CNAO Foundation in collaboration with the INFN.

1.3 Services delivered by CNAO: the integration between research and healthcare

The CNAO is a research and health care infrastructure with a double-sided interrelated and integrated goal, closely interlinked with each other. On one hand, it aims at treating patients with radio-resistant and unresectable solid tumours by using hadron particles (either protons or carbon ions) accelerated by

[11] Specifically, the energy range for protons is 60-250 MeV, the one for carbon ions is 120-400 MeV/u.

a synchrotron. On the other hand, the Centre aims at providing hadrontherapy advanced research in clinical, radiobiological and dosimetric matters.

Although being in principle two separate activities, clinical and research activities are strongly integrated inasmuch as they feed into each other in terms of generating and applying research and clinical evidence. Indeed, the experimental nature of hadrontherapy still requires extensive clinical and translational research which includes biology, medical physics and technology as well as advanced clinical research on diagnosis, prognosis, treatment, oncological outcome, morbidity and quality of life for various forms of malignancies (Pötter *et al*., 2013).
In particular, due to the high technological character of the facility, research activities are necessary to continuously improve the diagnostic and therapeutic instrumentation in order to optimise and improve the effectiveness of the therapy. In addition, by following-up all the patients after hadron-therapy at CNAO and in other hadron-therapy centres around the world, the effectiveness of the therapy is established and therapy protocols developed and/or improved and fine-tuned. In this sense, CNAO is an at-the-edge research facility.

CNAO Foundation, by its own statute, has scientific research as one of its fundamental goals. The high technology infrastructure existing in CNAO offers indeed unique possibilities to carry on scientific and technological research activities in the multidisciplinary fields connected to hadrontherapy.

Research activities carried out at CNAO are performed to develop projects and experiments in all scientific area involved in the Centre, with the strategic aim to develop and optimise the therapy. Specifically, research activities in the fields of clinical radiobiology, medical physics and high technology are conducted, either in collaboration with research institute such as INFN or CERN for the technological development or with clinical and health centres as far as clinical research is concerned. Research is not only carried out by staff working in the RI but also by a number of research teams of the universities and the research centres belonging to the CNAO Foundation. Moreover, a new research line is currently in the design phase. When it will be operational, it is expected that the beam could be provided to researchers in the framework of funded European projects as well as to other external paying users (including private companies) to carry out their own researches and tests.

2 Methodology

Cost-Benefit Analysis is an analytical tool aimed at informing decision making on the economic viability of projects, programmes, policies or regulatory initiatives by, first, identifying all the costs and benefits and, second, by measuring them through a monetary value of the welfare change attributable to them (Boardman et al. 1996, Florio 2014). The purpose of CBA is to support a more efficient allocation of resources demonstrating the convenience for society of a particular decision against possible alternatives (including the 'do nothing' or 'business as usual' alternatives).

CBA is grounded in welfare economics and is the solution of the government's planning problem of constrained optimisation of a social welfare function. Since its origin, at the beginning of the XIX century in the tradition of the French civil engineering school of public works, CBA has evolved over time undergoing different phases of experimentation, consolidation and diffusion in different institutional settings and sectoral traditions. However, while a well-established and widely accepted CBA analytical framework is available for transport, environment, energy and social infrastructures (culture and health) no established framework is available for research infrastructure yet.

The methodological framework adopted to assess the net welfare gain produced by CNAO is an adaptation by Florio and Sirtori (2014) to research infrastructure of the CBA theoretical framework developed by Drèze and Stern (1987, 1990). According to this theoretical model, benefits of research infrastructure can be summarised by equation (1). Following the equation, the expected net present value of research infrastructures ($ENPV_{RI}$) over the time horizon $\mathcal{T}$ is defined as the sum of all measurable benefits which are associated to any actual or possible use of the research infrastructure

$[S + T + H + C + A]$, plus a non-use (existence) value of scientific discover B_n, net of socio-economic costs $[K + L_s + L_o + O + E]$, valued at shadow prices[12] and discounted[13] at the social discount rate r.

$$ENPV_{RI} = [S + T + H + C + A] - [K + L_s + L_o + O + E] + B_n. \quad (1)$$

According to the formula, five main kinds of measurable benefits stem from any RI project. For applied research facilities the most relevant one is by far the benefits produced by the service provided by the infrastructure to its users (A): in the case of CNAO this refers to the effects on the health of treated patients, but for other facilities they may relate to environmental protection services (observatories studying natural hazards and technogenic risks), energy efficiency (centres carrying out research on renewable and efficient sources for the energy sector), testing of materials for private companies and license deals, etc. In the case of CNAO, in addition to patients, other external users of the facilities are scientists and industries who can benefits from the use of the beam line for research or technological development and testing purposes.

In addition to the benefits from the results of applied research, however, there are other benefits which are typical of research facilities. They are:

- knowledge output (S): this relates to the production and dissemination of new knowledge in a given scientific field, and it is typically related to scientific publications;
- technological spillovers (T): this is related to the transfer of knowledge related to the technological development and passed either to companies in the supply chain or to other similar research facilities;
- human capital accumulation (H): this relates to the training and educational benefits of students and professionals involved in research activities;
- wider cultural effects of the project outreach activities (C): in many cases, particularly when dealing with large and high-tech infrastructure projects, benefits are generated by activities addressed to the wider public and aimed at disseminating scientific knowledge through conferences, events and visits.

In the case of applied research facilities, and of CNAO in particular, the non-use value is less relevant and therefore it will not be considered in the present analysis.

According to this methodological framework, CNAO is assessed to produce net benefits to society if the sum of the net present values of the aforementioned categories of benefits outweigh its costs, including the use-costs related to the present value of capital K, labour cost L (including scientific personnel L_s and labour costs of other administrative and technical staff working at the RI L_o), other operating costs O, such as materials, energy, communication, maintenance, etc., and negative externalities E, like air pollution or noise during construction and operations.

A final key aspect of CBA is that, in order to account for the uncertainty related to the necessary forecasting exercise, estimated baseline values are linked to a probability of error and a range of variations instead of deterministic (punctual) values are considered. Whenever it is possible, a lower and upper bound around the baseline values have to be established. Alternatively, a deviation from the baseline can be estimated. Then the next step is to assign to each variable a probability distribution

[12] Shadow prices are values reflecting the opportunity cost of a good or service which is defined as the potential gain from the best alternative forgone, when a choice needs to be made between several mutually exclusive alternatives. The rationale for using shadow prices in place of observed market prices when evaluating the welfare impact of infrastructure projects relies on the fact that shadow prices better reflect the social marginal value of goods in an economy where markets are not perfectly competitive and efficient and prices are likely to be distorted.

[13] Discounting is a computation which enables to express future monetary or socio-economic effects in terms of present values when inter-temporal decisions are to be taken from 'today's viewpoint'. Since the timeframe of the analysis in CBA is usually of some decades, values accounted in different years can be summed up only after discounting them to present values. The rationale for discounting relies on the observation that the employment of resources has an opportunity cost, meaning that resources committed to a project could be employed in another return-generating investment. Moreover, consumers generally prefer to receive the same amount of goods and services sooner rather than later.

constrained by the distribution parameters previously defined (e.g. lower/upper bounds or deviation). A risk analysis with the Monte Carlo simulation techniques is then used to aggregate the probabilities assigned to the variables underpinning each type of benefits as well as future costs[14]. By drawing (without replacement) one value of each variable from the respective cumulative distribution function and plugging the extracted values into the CBA model, the net present value associated to the research infrastructure is computed. This process repeated over a large number of iterations allows to obtain a distribution of results from which the minimum, maximum, mean values and the standard deviation of the NPV can be calculated and compared with its reference value.

In line with the CBA standard framework, the analysis is carried out on the basis of the following considerations:

- the unit of analysis is the CNAO in its totality. The infrastructure taken into account is not only the hall hosting the particle accelerators but also the other areas functional to the proper functioning of the clinical facility. It also includes the new research line facility and related room.
- All costs and benefits are estimated in incremental terms against a counterfactual scenario in which the CNAO would have not existed (do-nothing option). In this particular case both a "Business as Usual" and a "Do-minimum alternative" are not relevant.
- The analysis starts in 2002 (year 0), after the CNAO Foundation was established by the Italian Ministry of Health and the investment officially approved. In particular, 2002 is the first year when investment costs occurred.
- The analysis spans up to 2031. The end year has been set considering the useful life of the CNAO accelerator. Specifically, it has been set according to the criterion that when the extraordinary maintenance of the machine became so frequent and expensive that replacing it with a new one is more convenient, the machine has arrived at its ending. Also, considerations in terms of advancement in the field of cancer care and subsequent possible obsolescence of CNAO methods have been taken into account. As a result, a time horizon of 30 years has been considered the most appropriate. However, it is worth mentioning that knowledge creation and human capital benefits give rise to economic inflows which extend even beyond the CNAO useful life (see next sections).
- The analysis is carried out from the perspective of year 2013, thus it is neither a pure ex-ante nor an ex-post evaluation. Instead, it entails both to track historical data and to project future flows of costs and benefits. Costs and benefits have been quantified and valued in Euro at 2013 constant prices[15].
- A constant 3% Social Discount Rate, in line with the provisions for CBA of major projects adopted by the European Commissionfor the programming period 2014-2020, has been applied to capitalise past flows and discount future flows[16].

In the following sections baseline and ranges associated to the key quantities associated to costs and benefits of CNAO are identified, quantified and monetised.

[14] If a *mid-term* CBA is performed the past capital and operating costs are not stochastic variables and therefore are not considered in the risk assessment.

[15] This implied to bring past nominal cost to 2013 value: to this end, an inflation factor, estimated on the basis of annual inflation rates for Italy (source: IMF), has been applied to past values.

[16] The social discount rate (SDR) is used in the economic analysis of investment projects to discount economic costs and benefits, and reflects the opportunity cost of capital from an inter-temporal perspective for society as a whole. In other words, it expresses the rate at which society is willing to postpone a unit of current consumption in exchange of more future consumption. In this sense, every discount rate entails a judgment concerning the future and it affects the weight attributed to future benefits or costs.In most of CBA practice, a constant discount rate is used, which implies an exponential discounting process of the project's inflows and outflows. This means that benefits occurring far in the future are discounted more than costs of investments, which instead usually take place in the initial years of the time horizon.

3 Costs

The cost side of the analysis should include the capital cost of the investment and operating cost valued at shadow prices, plus negative externalities and other non-market negative effects. In this section the costs sustained for the construction of the CNAO as well as those paid for its operation and maintenance are presented.

The production of the technical specifications which led to the construction of CNAO was the result of a major collaborative research effort involving a number of universities and institutes. TERA Foundation under the leadership of Ugo Amaldi has been working on projects for designing an Italian centre for Hadrontherapy since 1991[17]. In the years 1992-2002 TERA in collaboration with the National Institute of Nuclear Physics, several Universities, CERN and GSI designed three different synchrotrons to be used for the treatment of deep seated tumours with beams of protons and carbon ions. On the basis of a Memorandum of Understanding, one of these designs was consigned to the CNAO Foundation which was promoted by TERA and established by the Italian Health Ministry in 2001. Indeed, at the end of 2002, TERA gave to CNAO 3,000 pages of specifications and technical drawings, 16 employees and 9 collaborators. They form the core group of the CNAO staff which has streamlined the project design and constructed the Centre in Pavia. The project has been indeed self-commissioned as well as realised mostly "in-house" by CNAO staff, with an approach that enabled savings on construction costs and, at the same time, established high professional competencies.

The present analysis starts in year 2002 when CNAO was established. Costs incurred in the past mainly by TERA Foundation in connection with the project under assessment are considered as sunk costs and, as a consequence, ignored. However, the costs related to the purchase of the design works by the TERA Foundation are actually part of the investment costs. In this way, only the costs directly related to the construction of the CNAO are considered and compared to benefits, while the broader costs incurred during the long exploratory period of development of project ideas, which included also design works which did not actually materialise in realisations at the CNAO are disregarded.

Table 1 Investment costs (Non discounted)

Asset	Million Euro	Share of total
ASSET ACCELERATORS[18]	53.8	33.8%
ASSET BUILDING AND AUSILIARY SISTEMS[19]	49.9	31.3%
ASSET MEDICAL DEVICES[20]	17.1	10.7%
ASSET IT network and others	2.9	1.8%
TOTAL COSTS OF ASSETS	**123.6**	**77.6%**
OTHER COSTS in the investment phase[21]	35.6	22.4%
TOTAL INVESTMENT COSTS	**159.3**	**100%**

Source: Authors elaboration based on CNAO data. 2013 constant prices.

The investment costs include the capital costs of all the fixed assets (e.g. land, constructions buildings, plant and machinery, equipment) and non-fixed assets (e.g. start up and technical costs such as design/planning, project management, construction supervision). In other words, the CNAO

[17] The Hadrontherapy Programme was initiated in spring 1991 and the TERA Foundation was created in fall 1992 to collect funds and employ a staff of fully devoted to Hadrontherapy Programme with the aim to bring Italy to the forefront of tumour radiotherapy by the beginning of 2000. From the beginning of 1992, TERA was engaged in the design and realisation of a hadrontherapy centre based on a synchrotron which can accelerate protons at least 250 MeV and carbon ions to at least 4500 MeV.

[18] Initial project (TERA), Control system, Conventional magnets, Feeders, Special magnets, Vacuum system, Beam diagnostics, Injector, Sources, RF cavities, Betatron magnet, Scanning System (Nozzle Assembly), Security system, Miscellaneous (wiring, mechanics).

[19] Building works, Land, Electrical systems and cabin, Mechanical systems, Transmission systems, Furniture, Construction management and design.

[20] Imaging, OIS, PPS, TPS

[21] Energy, personnel, administrative, consumable goods costs, during the construction phase.

investment costs comprise the costs for designing and building the assets, i.e. the accelerators, the building, the medical devices and the IT network, as well as other costs such as energy, personnel, administrative consumable goods costs occurred during the construction phase. These categories of costs span form 2002 to 2013, which is the investment period.

Operating costs are instead all the costs to operate and maintain the Centre after the construction. They include: labour costs for the employees; materials needed for maintenance and repair of assets; consumption of raw materials and energy; general management and administration. These categories of costs span from 2011 up to 2031 which is the end of the time horizon considered for the analysis. Estimates of future values are based on the observation of historical costs and on the consideration of forecasts of future personnel involved and direct costs related to the number of patients, as well as a periodical renewal of spare parts for maintenance activities.

Table 2 Operating costs (Non discounted)

Item	Million Euro	Share of total
Direct costs for clinical activity	16.6	5.3%
Fluids and energy consumption	57.5	18.2%
Personnel costs	151.4	47.9%
General and administrative expenses	39.7	12.6%
Maintenance	50.6	16.0%
TOTAL OPERATING COSTS	**315.8**	**100%**

Source: Authors elaboration based on CNAO data. 2013 constant prices.

Besides investment and operating costs, replacement expenditures and future investment costs have to be considered. The former include costs occurring during the reference period to replace short-life machinery and/or equipment such as beam sources and detectors. The latter refers to future costs mainly associated with the construction of the research line. As previously mentioned, this line was expected since the beginning of the CNAO construction and its realization is planned to occur from summer 2014 to 2017. This relative long period of construction is due to the fact that the works concerning the accelerator and the auxiliaries or the rooms that house them have to be carried out when there are no clinical activities, i.e. during the weekend and during the nights. The construction of the research line is expected to cost nearly 9 million Euro, which represents a preliminary estimate for basic components. Timing of construction is strictly dependent on public funding, grants, or credit facilities. In addition, a constant activity of upgrading and optimisation of technological instruments, costing nearly 1 million per year, is undertaken, in line with the at-the-edge nature of the activities carried out in the Centre.

As a result, the total cost considered for the purpose of the Cost-Benefit Analysis of the CNAO amounts to 465.9 million EUR over the 2002-2031 period, expressed at 2013 constant EUR, discounted at a 3% social discount rate. The total amount includes the decommissioning costs (nearly EUR 4 million expressed at 2013 constant EUR, discounted), calculated as a share (10%) of the accelerators and building total investment costs.[22]

Table 3 Summing up costs

	Total CNAO cost Non discounted (M EUR)	Total CNAO cost Discounted (M EUR)
Past investment cost, 2002-2013	159.3	188.8
Future investment cost, (including research line) 2014-2031	28.6	23.8
Operating costs (2011-2031)	315.8	248.5
TOTAL	**511.7**	**465.9**

Source: Authors elaboration based on CNAO data. 2013 constant prices. Note: Total amount includes decommissioning costs

[22] Excluding cost items referred to Initial project, Land, Furniture, Construction management and design.

4 Applied research benefits on patients

Being CNAO conceived to supply hadrontherapy treatments to persons affected by radio-resistant and unresectable solid tumors, the most relevant benefit associated with this infrastructure refers to the health improvement on treated patients. Typical health benefits associated to clinical activities are decrease in mortality rate and increase in the life expectancy suitably adjusted by the quality of life. While these benefits are typical of all health infrastructures, the specificities of CNAO is the inherent capacity to expand the scientific knowledge on the clinical benefits of hadrontherapy which can be immediately translated into the development of new innovative protocols optimising the existing treatment services or developing brand new ones. Therefore, the benefit is intrinsically inherent in both clinical activity and the research carried out.

However, while proton therapy is a usually considered a conventional clinical activity (although technological development is also possible, for example as far as imaging and scanning instruments are concerned) and can be carried out routinely in many other health centres worldwide[23], carbon ion therapy shows promising applications which are still at the experimental phase and need research activities which can be immediately translated into the development of innovative clinical protocols optimising the existing treatment services or developing brand new ones and which would not be carried out in a traditional health centre. As a result, health benefits associated to the medical services provided at CNAO can result from a more or less experimental therapy. In this sense, with some approximations, it is possible to distinguish between conventional health benefits associated to proton therapy and applied research benefits associated to carbon ion therapy.

Empirical testing shows that the magnitude of this *A*-benefit is by far greater than any other item in the Equation (1). In particular, the share of the benefit associated with the carbon ions represent the largest part of the total benefit. This is in line with the nature of applied research infrastructure of CNAO, where knowledge and technologies developed by the particle physics scientific community is used for delivering oncological treatments which, thanks to the advancement of knowledge in the research field, are more effective than existing treatments.

Valuing this benefit implies, first, to calculate the total number of patients and the breakdown by the different clinical treatments, the health benefits associated to a higher effectiveness and lower toxicity level for each category of patients and, finally, the estimation of the economic value of life. In particular, the following formula applies:

$$A = \sum_t^T \frac{\sum_p^P \sum_i^I \left(N_{p,\ i} * E_p\right) * \left(X_{pi} * VOLY_i\right) * Q_p}{(1+3\%)^t} \qquad (2)$$

Where:
N: number of patients
E: share of patients who gain additional years of life compared to the identified counterfactual
X: number of life years gained
$VOLY$: Value of Statistical Life Years
Q: coefficient capturing the increased quality of life
p (1, ..23):clinical protocol
i (1, ..6): age class
t (1, …30): year of time horizon

The estimation of each component of the formula is discussed in the following sections.

[23] Since 1990 around 110,000 patients have been treated worldwide with proton. At present, 45 proton facilities are in operation worldwide, 24 are under construction and 16 in the design phase See PTCOG website. Last update: 09-Nov-2014.

4.1.1 Patients quantification

According to estimates, during routine operation, at CNAO nearly 1,000 patients per year will be treated in the baseline scenario. However, since the Centre will run at full capacity only from 2020 onwards, an increasing trend of total patients has been assumed from 2015 to 2019[24].

Under the assumption that during routine operation CNAO can treat around 1,000 patients per year and given the country demand forecast for protons and carbon ions therapy provided by the Italian Association of Radiation Oncology (AIRO)[25] and the existing and future national supply[26] of hadrontherapy treatments, the yearly number of patients for each protocol has been estimated. In addition, the total yearly number of patients under each protocol has been split by six age-class using historical data as well as opinions of the CNAO medical staff. The following table provides an example on how patient data have been organized.

Table 4 Patient data breakdown by years, protocols and age-class

Protocol	Age-class	2011	2012	2013	2014	…	2020	…	2031	Total
Protocol 1	15-25 (20)	-	2	1	1	…	1	…	1	**26**
	26-38 (32)	1	2	1	1	…	2	…	2	**33**
	39-52 (46)	-	9	4	1	…	5	…	5	**93**
	53-66 (60)	-	5	5	3	…	5	…	5	**86**
	67-80 (74)	-	8	5	-	…	5	…	5	**86**
	81-95 (88)	-	-	-	-	…	-	…	-	**0**
Protocol 2	15-25 (20)	-	-	-	-	…	-	…	-	**-**
	26-38 (32)	-	1	-	-	…	1	…	1	**14**
	39-52 (46)	1	1	1	1	…	3	…	3	**57**
	53-66 (60)	-	4	2		…	5	…	5	**85**
	67-80 (74)	2	5	2	1	…	8	…	8	**142**
	81-95 (88)	-	-	-	-	…	-	…	-	**-**
Protocol *n*…		…	…	…	…	…	…	…	…	**…**
Total		**4**	**46**	**134**	**253**	**…**	**1,000**	**…**	**1,000**	**16,735**

Source: Authors based on AIRO and CNAO data

For the purposes of the analysis, a uniform probability distribution function has been assigned to the variable "number of patients". Specifically, a lower and upper bounds of, respectively, 600 and 1,200 have been considered. The curve obtained is shown in the following figure.

4.1.2 Marginal health improvements

Being proton therapy more widespread and consolidated with respect to carbon ion therapy a wider literature on its toxicity effects and effectiveness in comparison to other radiotherapy techniques such as conventional radiotherapy and stereotactic surgery is available (e.g. Fossati *et al.*, 2009). Although still growing and limited in number, phase III studies (those which compare toxicity rates or local control and overall survival of ions, protons and photons) are finally ongoing, and several results are now available; on the other hand, the current phase I and II clinical results (see for instance Kamada *et al*. (2002), Shulz-Ertner *et al.*, 2007) support the rationale of both proton and carbon ion therapies, especially for tumors localized in proximity of critical organs, unresectable or recurrent tumors, and in general tumors resistant to radiation due to histology, genetic background and/or local microenvironment, including hypoxia (NuPECC, 2013). Therefore, hadrontherapy is currently indicated for people affected by chordomas and chondrosarcomas of the skull base, soft tissue and bone sarcomas, large uveal and mucosal melanomas as well as most of the pediatric patients eligible for conventional radiotherapy.

[24] Different protocols have different increasing trend.

[25]The study prepared by the "Group of study on the Hadrontherapy - Implementation of a network of clinical centres over the Italian territory" presents the estimations of the total number of patients eligible for protons and carbon ions therapy in Italy.

[26]A proton centre for ocular melanoma already exists in Catania and a proton centre has been recently opened in Trento.

To date, CNAO can treat clinical cases falling under 23 clinical protocols[27] authorized by the Ministry of Health and activated by the Centre. Of which 12 uses carbon ions, 9 protons and 2 are mixed. Other four protocols are currently awaiting approval. However, for the purposes of our analysis only the 23 protocols already approved have been considered. Each protocol is associated to a specific treatment addressed to a specific type of tumor in a determined organ. Therefore, treatment effectiveness and, in turn, the health improvement is strictly linked to the type of protocols considered. For the purposes of our analysis, three types of benefits have been identified and linked to each treatment provided at CNAO (See Table 5).

Table 5 Types of benefits[28]

TYPE	DESCRIPTION	COMMENT
TYPE 1	Full recovery of patients	The treated patients gain the same life expectancy of the average healthy population
TYPE 2	Treated patients gain some additional year of life	This benefit can also be combined with an effect on the quality of life, i.e. the patient can enjoy fewer side effects with respect to the ones occurring with a counterfactual treatment during the additional years of life gained.
TYPE 3	Better quality of life (i.e. lower level of pain and suffering)and no effect on the life expectancy	A better quality of life means that the patients can enjoy fewer side effects such as vomiting, nausea, fatigue, dermatitis, headaches, during the treatment time or the additional years of life gained thanks to the therapy. The lower level of side effects is due to the lower toxicity of the hadrontherapy treatment with respect to the conventional photon treatment. In addition to this, better quality of life is also linked to the fact that, compared to more traditional treatments, there is a reduction in the length of the therapy, with a reduction of all the related costs.[29]

Source: Authors

Following the indications by the CNAO medical staff, each protocol has been associated with one of the mentioned types of benefits (see the table below). When consolidated evidence on effectiveness was not available for the experimental nature of the treatment, a conservative approach was followed and a prudential identification of benefits of type 2 and 3 was indicated[30]. Furthermore, the identification of a counterfactual scenario for each type of protocols was necessary in order to quantify the marginal benefit associated to the hadrontherapy treatment[31], in particular for what concerns the number of years gained and for the degree of effectiveness (percentage of successful treatment) for each protocol.

For the large majority of protocols the counterfactual is the "do-nothing" since they refer to patients that have no treatment alternative. In other words, most of the patients falling under protocols activated by CNAO are those for whom there are no other clinical alternative either because they have been already treated with an alternative therapy which actually proved not to be successful or they have radio-resistant tumours. In other cases the counterfactual is an alternative treatment depending on the pathology: surgery, photon therapy (i.e. conventional radiotherapy), a combination of the two above and chemotherapy. Clearly, benefits are maximised when the counterfactual situation is the "do-nothing", since in those cases the overall gain due to the therapy coincides with the marginal gain.

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[27]Clinical protocols are documents with the aim of guiding decisions and criteria regarding diagnosis, management, and treatment in specific areas of healthcare. Dosimetry protocols, i.e. documents which according to the machine used define methods and concepts for irradiation doses and tumour volumes, are of paramount importance in the hadronterapy field.

[28] For prudence, such benefits do not include the decrease in the occurrence of secondary cancers in young treated patients as compared to conventional treatments

[29] For the time being this additional benefit has not been estimated yet, for conservatism and easiness of analysis at this stage.

[30] If such experimentations are successful, as expected, those benefits are expected to increase accordingly and, possibly, to be of type 1.

[31] The counterfactual scenario for each protocols has been established based on extensive interviews with the medical staff of CNAO.

Once the counterfactual treatments have been identified, the quantification of the marginal benefit arising from each protocol has been calculated. In order to do this, the data on the local control and the rate of overall survival at different years after the treatment have been collected for each type of protocols/tumours as well as for both the hadrontherapy and the counterfactual treatments. The last columns of the following table summarises the marginal benefits associated to each protocol which have been thoroughly discussed with the CNAO medical staff.[32]

Table 6 Marginal benefit by protocols

#	Pathology	Clinical alternative	Type of benefit	Marginal percentage of patients who fully recover compared to the counterfactual situation identified in column 3 (for benefit of TYPE 1)	Number of life years gained thanks to hadrontherapy with respect to the counterfactual situation identified in column 3 (for benefit of TYPE 2)
1	Proton radiation therapy for chordomas and chondrosarcomas of the skull base	No alternative	TYPE 1	73%	-
2	Proton therapy of spine chordoma and chondrosarcoma	No alternative	TYPE 1	73%	-
3	Proton therapy of intracranial meningioma	No alternative	TYPE 1	33%	-
4	Proton therapy of brain tumors	No alterative*	TYPE 3	-	-
5	Proton therapy of recurrent cervico-cephalic area tumors	No alterative*	TYPE 3	-	-
6	Proton boost for locally advanced cervico-cephalic area tumors	No alternative for advanced tumours	TYPE 2	15%	5
7	Proton therapy of glioblastoma	No alterative	TYPE 3	100%	1
8	Proton re-irradiation of recurrent spine chordoma and chondrosarcoma	No alterative	TYPE 2	43%	3
9	Carbon ion therapy of adenoid cystic carcinoma of salivary glands	Surgery + photon therapy	TYPE 1	45%	-
10	Carbon ion re-irradiation of recurrent pleomorphic adenomas	Surgey	TYPE 1	21%	-
11	Carbon ion re-irradiation of recurrent rectal cancer	No alterative*	TYPE 1	45%	-
12	Carbon ion radiotherapy for bone and soft tissue sarcoma of cervico-cephalic area	No alterative*	TYPE 1	14%	-
13	Carbon ion radiotherapy for bone and soft tissue sarcoma of trunk	No alterative*	TYPE 1	33%	-
14	Carbon ion therapy of recurrent cervico-cephalic area tumors	No alterative*	TYPE 2	68%	0.5
15	Carbon ion therapy of malignant melanoma of the mucous of the upper aerodigestive tract	Surgery + photon therapy	TYPE 1	30%	-
16	Carbon ion therapy for high risk prostate cancer	Photon therapy	TYPE 1	43%	-

[32] Lacking established evidence on the effectiveness of some of the treatments provided at CNAO due to their innovative nature the estimation of benefits illustrated here follows a conservative approach inasmuch as the identification and quantification of benefits relies by far on existing medical literature on effectiveness of more traditional therapy, in some cases adjusted with 'best guess' provided by physicians of CNAO.

17	Carbon ion therapy of primary and secondary orbital tumors	Surgey	TYPE 3	-	-
18	Carbon ion therapy for pancreatic cancers	Palliative chemotherapy	TYPE 2	40%	2
19	Carbon ions therapy of primary malignant tumors of the liver	Photontherapy	TYPE 1	36%	-
20	Carbon ion re-irradiation of recurrent spinal chordoma and chondrosarcoma	No alterative	TYPE 2	43%	3
21	Proton therapy of eye melanoma	Surgey	TYPE 3		
22	Protons and/or carbon ion integrated radiotherapy for poor prognosis in patients with operable sinonasaltumor	Surgey + photon therapy	TYPE 2	10%	5
23	Protons and/or carbon ion integrated radiotherapy for poor prognosis in patients with inoperable sinonasaltumor	Photontherapy*	TYPE 2	35%	5

Source: Own elaboration based on interviews with CNAO medical staff. Note: (*) No alterative since the patients considered under this CNAO protocol are those who cannot be operated.

As for the quantification of the benefit related to the improvement of the quality of life, a quality factor ranging from 0 to 1 and that reflect individuals' perceptions of the quality of life associated with both the hadrontherapy and the counterfactual treatments have been identified when enough data were available. When possible, the quality factors have been quantified based on the matrix of performance status developed by Karnofsky (Karnofsky and Burchenal, 1949).

In order to take into account the uncertainty associated to the effectiveness of treatments, a range of variation associated to the marginal benefit arising from each protocol has been considered instead of punctual values. In particular, a standard deviation of 0.1 around the modal values presented in the table above has been used in the analysis.

4.1.3 The economic value of life

Regardless from the particles used, which in turn means different level of experimentation and proved effectiveness, health benefits associated to clinical activities are decrease in mortality rate and increase in the life expectancy suitably adjusted by the quality of life. There is a vast and well-established literature on the economic value of statistical life (e.g. Landefeld and Seskin, 1982, Viscusi and Aldy, 2003, Abelson, 2008 and 2010, Sund 2010). Following the literature, the monetisation of an increase in the life expectancy encompasses the estimation of the Value of Statistical Life (VOSL) and the related Value of a Life Year (VOLY). The former is defined as the value that society deems economically efficient to spend on avoiding the death of an undefined individual (Sund, 2010). The latter represents, instead, a constant value to be attributed to each life year lost due to premature death. The VOLY and the VOSL are related as follows:

$$VOSL = \sum_{t=1}^{T-a} VOLY * (1+r) \qquad (3)$$

Where a is the age of the individual or group considered, T is the life expectancy and r is an appropriate discount rate. However, in the absence of direct empirical estimates of the VOLY, it is usually derived from the VOLS calculated as a discounted stream of annual life year values over the remaining lifetime of the subject, adjusted by the survival probabilities (European Commission, 1999).

Different methods of measuring or approximating society's willingness to pay for reducing the risk of death exist, ranging from contingent valuation survey to benefit transfer, from cost of illness to human capital approach (see, for instance, Viscusi and Aldy, 2003; Ashenfelter, 2006; Sund, 2010; OECD, 2010, 2012). Most WTP values for a reduction in the risk of death are derived from contingent evaluation surveys. Here, individuals are asked hypothetical questions on what they are willing to pay in exchange of a risk reduction. In spite of being widely used this approach is also quite controversial. Indeed, it is associated with the risk that respondents may not give accurate answers or, even worse, the risk that people provide fake answers since they have incentive to free-ride in order to increase the chances of provision of the desired good without having to pay for it (Carson and Groves, 2007).

With the attempt to address such shortages revealed-preference approach has been used in some studies. This approach uses market data on observed behavior among individuals to estimate implicit WTP for changes in mortality risks. The most explored market is the labour one, where wage premiums are offered to workers to accept more risky jobs. In other words, workers are assumed to be willing to forego income from improved workplace safety or to accept income for taking more risk. Even this approach is not without critics. The main problem deals with the fact that wage premiums may not reflect risk preferences due to information asymmetry or significant imperfections in the labour market such as unbalance in the bargaining power.

Studies which have estimate a VOLS using either the revealed or the stated preference approaches have come up with a wide range of values. Viscusi and Aldy (2003) which reviews a large number of studies using US labour market data shows that VOSL is typically in the range of US$ 4 million to US$ 9 million (level in 2000 dollars). Mrozek and Taylor (2001), which carried out a meta-analysis on several revealed preference studies, estimated that VOSL for an unforeseen death is about US$ 2.5 million. A comprehensive meta-analysis has been recently carried out by Braathen at the OECD (2010, 2012), who collected all the published values for statistical life calculation by contingent valuation methods. From this study it is particularly striking the variability of estimates of statistical life associated with health risks. The mean VOSL for health risks is nearly US$ 2.5 million (level in 2005 dollars) which is nearly more than twice the median value of the sample.

Contrary to the high VOSL estimates associated with either the revealed or the stated preference approaches the ones associated to the human capital (HK) approach are usually lower. This approach, which has a long history dating back the mid-1960s, assumes that the value to society of an individual's life can be measured as the present discounted sum of the individual's expected labour earnings. By its emphasis on economic products, this approach give, in principle, a zero value for persons without labour income such as young people and ignores factors such as pain, suffering, loss of leisure and aversion to risks which have value for an individual as well. Nevertheless, the human capital approach claims its relatively simple operationalization. This feature can be a strong advantage in those cases where constraints in terms of time and resources hamper the application of most sophisticated techniques such as contingent valuation and market analysis.

Following the human capital approach, the VOSL based on the lost production in terms of average annual wage due to a premature death of an individual is calculated for the CNAO patients. Specifically the following formula applies:

$$\text{VOSL} = \Sigma_{i=1,T-t}(p_{t+1}\,Y_{t+1})/(1+r)^i \quad (4)$$

where $\Sigma_{i=1,T-t}$ denotes the sum over time from time t (the current age of the individual at risk), T is the age at which the individual is expected to die, p_{t+1} is the probability of the individual surviving from age t to age t+i, $Y$is the per capita average annual wage, and r is the discount rate.

Evidence from the literature shows that by convention the VOSL is usually assumed to be the life of a young adult with at least 40 years of life ahead[33]. According to this, a VOSL equal to EUR 1,030,000 has been estimated for a person aged 20 year old. The baseline assumption is that the individual can potentially contribute to the social community until the age of 62[34].This VOSL has been obtained as the sum of discounted value of labour income the individual is expected to receive until the pension age, by applying a social discount rate specifically calculated for Italy. Then, a constant VOLY equal

[33] See for instance Abelson (2008)
[34] At present, in Italy people can retire after 42 years of work.

to nearly EUR 23,200 has been derived from the calculated VOSL(20). The utilization of a constant VOLY with respect to age can be controversial (see for example Abelson, 2010). Indeed, as long as the VOLY is constant, a treatment that saves *n*-young adults, who have a longer life expectancy with respect to *n*-individuals, would lead to greater benefits.

Although accepted as a rule of thumb, this approach presents some shortcomings. As mentioned, it focuses only on the active working population and ignores the value of life of individuals which are excluded from the labour market. In order to mitigate such limit a slightly different approach to the standard human capital method has been applied. In particular, based on the above formula the VOSL is calculated consideringper capita GDP instead of average annual salary as a measure for the lost production due to a premature death of an individual. Since per capita GDP is a measure of gross domestic output attributable to each individual within a country, it can be considered a proxy of individual production value (see Jongejan *et al*., 2005 and Vrijling *et al*., 1998).

Specifically, equation (4) has been calculated for each of the six classes of age identified. As a result, six-age-related VOSL values have been estimated. From these values age-dependent-VOLYs have been derived. The average estimated values are presented in the table below.

Table 7 Value of VOSL and VOLY for the six considered classes of age (EUR, 2013 constant price)

VOSL Class	Value of VOSL	VOLY
VOSL (20)	1,156,067	26,036
VOSL (32)	972,568	25,568
VOSL (46)	734,126	24,934
VOSL (60)	467,450	24,117
VOSL (74)	172,048	22,614
VOSL (81)	21,567	21,811

Source: Authors

A benchmark analysis with WTP values available in the literature for a reduction in the risk of death confirms that the VOSL values estimated with the human capital are lower than those based on WTP.

Table 8 Benchmarking VOSL value

Country	Approach	VOSL value (EUR 2013)	Source
Italy	HK with wage pc	1,030,000	Own estimation
Italy	HK with GDP pc	1,160,000	Own estimation
Italy	WTP	1,836,524	Alberini and Chiabai (2006)
EU average	WTP	1,304,074	European Union (2001)
World	WTP – meta analysis	1,749,653	OECD (2010)

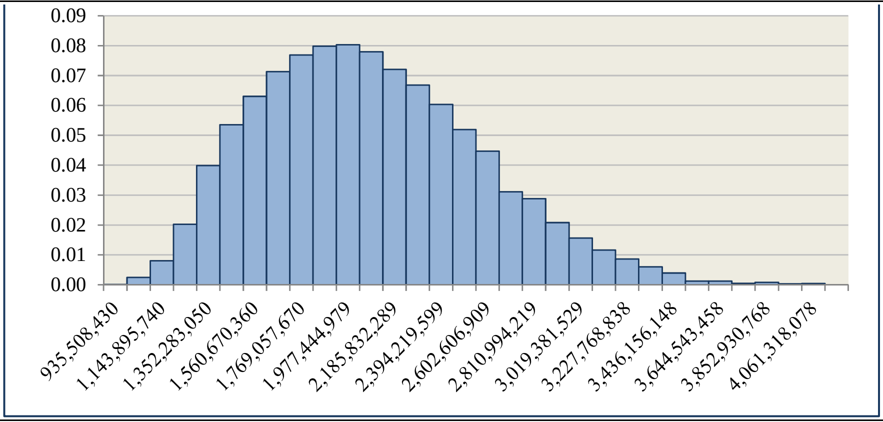
Source: Authors elaboration based on the sources provided in the last column of the table.

The benchmarking exercise presented in the table above has been exploited in order to set a range of variation for the VOSL value to be used in the analysis. Specifically, a triangular probability distribution function with lower bound of EUR 1,030 thousand, a modal value of EUR 1,160 thousand and an upper value of EUR 1,800 thousand has been considered. The lower bound value is set equal to the result of VOSL calculated with the human capital approach based on the lost production in terms of average annual wage. The modal value equals the result of VOSL calculated the human capital approach based on the lost production in terms of per capita GDP. Finally, the upper bound is set as the VOSL value calculated with a benefit transfer approach from the WTP value reported in Alberini and Chiabai (2006).

4.1.4 Benefits on patients

Having established the range of variation of the three input variables needed for the health benefit calculation, i.e. the economic value of life, the marginal health improvement associated to each protocol and the number of patients treated, the total health benefit due to CNAO activity on patients has been estimated. The total expected present value of the applied research benefit on patients amounts to nearly EUR 2 billion, with ranges of possible values between nearly EUR 0.9 and 4.1 billion. Although with a large variation, health benefits are quite significant and even their estimated minimum value already pay off the total discounted costs.

Figure 2 Probability distribution of applied research benefits on patients (Euro)



Estimated parameters of the distribution

Mean	2,028,626,666
Median	1,984,699,763
Standard deviation	495,675,860
Minimum	935,508,430
Maximum	4,061,318,078

Source: Authors

5 Use of experimental beam line

Besides health benefits on patients, the possibility to use the beam line of CNAO for research experiments led to the rise of an additional source of *A*-type benefits, i.e. that linked with the services provided by the infrastructure to third users. A high or medium energy experimental beam line is strongly demanded by researchers pertaining to different fields: from radiobiology, dosimetry, accelerator physics, beam monitoring and diagnostics, clinical and translational research, up to bioengineering and industrial applications (e.g. radiation hardness studies, space radiation research, development and material characterization). Actually, the functional specifications of CNAO experimental beam line have been inferred from an on line survey, distributed among the scientific and industrial communities. The respondent researchers are the potential final users of the beam and their answers represent the real needs to be fulfilled by an experimental beam line, in terms of ion species to be accelerated, field size required for samples, energy ranges, time slots for irradiations and beam time per year. According to a survey around 20 institutions including research centres and universities have expressed their interest in using the CNAO's beam.

At present, the possibility to use the beam line of the CNAO for research experimentsis constrained by the priority given to clinical treatments in the use of the available beam line. However, as soon as the new beam line dedicated to research will be in operation, the use of the beam line for experimental purposes will become a steady service offered by CNAO to third users.

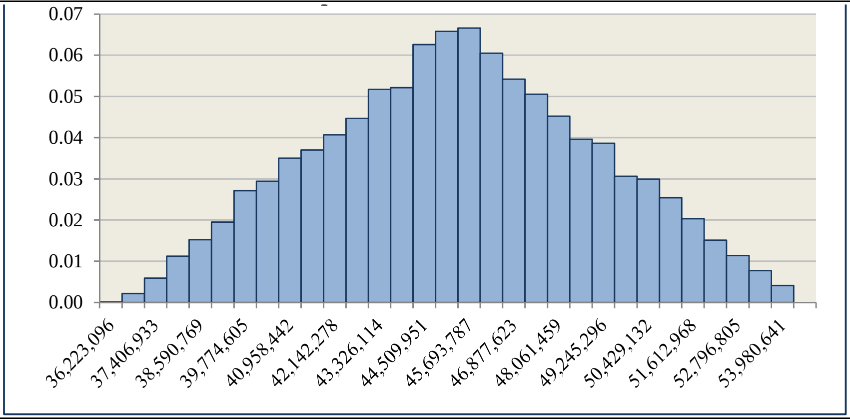
External users will pay a fee for the use of the beam, which has been estimated prudentially by CNAO as triangular distribution ranging from 2,000 to 3,000 EUR/hour with a mode of 2,500 EUR/hour[35].

[35] The cost will be probably revised in the future.

These figures have been estimated as the costs incurred by the facility to make the beam line available, so it is considered to be a good proxy of the long run marginal cost of the service.[36]

Considering a use of the beam of 8 hours a day for a number of days ranging from 200 to 225 per year[37] after 2017[38], the expected present value of the benefit spilling-over from the use of the research beam is nearly EUR 45 million.

Figure 3 Probability distribution of the use of experimental beam line



Estimated parameters of the distribution

Mean	45,116,395
Median	45,099,246
Standard deviation	3,651,365
Minimum	36,223,096
Maximum	53,980,641

Source: Authors

6 Value of knowledge outputs

As a research infrastructure, new knowledge generated at CNAO has spawned a stream of specialized literature. Students, scientists, medical and even technical staff involved in clinical and research activities publish the results of their research on specialised journals. Following Florio and Sirtori (2014), the first wave of this literature which may take the form of internal technical reports, preprints, research papers in scientific journals and research monographs is produced by all those scientists who directly use the RI and are involved in its operation and in the interpretation of first hand evidence. These are referred as ‘insiders’. Besides them there is the rest of the scientific community, including scientists working in other fields, who use the evidence provided, explained and discussed in the insiders’ papers, to produce other knowledge, referred as ‘second round’ knowledge outputs. The findings of these ‘second round’ outputs can, in turn, be used as a basis to produce other knowledge by other ‘outsider’ scientists. Thus, other waves of knowledge production can follow, and so on.

The quantification of preprints, publications, conference proceedings and any other product of knowledge produced by CNAO insider scientists and those ascribed to outsider scientists is the first step needed for the evaluation of the knowledge output. Scientometric techniques, analysing the patterns of the scientific literature generated over time around the CNAO have been exploited to associate a measure of scientific output to the RI[39]. In practice, tracking knowledge output resolves in quantifying the knowledge outputs generated by the RI insiders (taken as level 0), papers written by other scientists and citing those of the insiders (level 1), other papers citing level 1-papers, and so on.

[36] For this reason it is used as shadow price. Indeed, Drèze and Stern (1987, 1990) prove that, in some cases, the shadow price of a good can coincide with its long run marginal cost of production, i.e. the social cost of increasing the production of that good by one additional unit, holding the production level of all other goods constant.
[37] A trapezoidal probability distribution function ranging from 200 to 225 days per year with modal values of 210 and 225 has been used.
[38] The research line will be operative from 2018 onwards.
[39] These techniques are discussed in Carrazza, Ferrara and Salini (2014).

While the use of scientometric techniques is a well-established approach to provide quantitative characterization of scientific activity, relying publication records available in online repositories may lead to bias when the dominant mode of production in a specific scientific domain is not the journal article. The limited coverage of particular scientific fields by reference databases is a well-known issue in some specific disciplines such as social sciences and humanities (see Hicks, 2004, and Nederhof, 2006), law and computer science where peer-reviewed conferences are a major form of communication. The same coverage issue seems to apply for the particle therapy field. Indeed, the dissemination of knowledge within the scientific community of particle therapy is, until now, by large channelled through conference proceedings and informal exchange at dedicated events rather than through journal publishing. This practice poses specific challenges in terms of tracking and quantification of produced knowledge as compared to more conventional measures captured with traditional scientometric tools. In addition to that, particle therapy scientific community is relatively 'small' and rather young, therefore dedicated channels are still under development or relatively new. For instance, the International journal of Particle Theraphy[40] had a first issue only on Summer 2014.

Bearing in mind the mentioned caveats, scientometric analysis was complemented by a more detailed analysis of unpublished scientific outputs. Specifically, the bibliographic database used in the current analysis was a combination of records extracted directly from the INSPIRE[41], PubMed[42], Web of Science[43] websites by querying the public user interface. In addition, unpublished outputs such as conference proceedings made available by CNAO internal archive as well as founded in thematic websites such as PTCOG[44] website were taken into account and included in the database. Thanks to this approach we got the past trend of knowledge output associated to CNAO.

To establish future projections of the first level papers (L0) it was adopted a non-linear model which assumes a peack in the number of papers in 6 years when the CNAO exits from the initial experimental phase, i.e. 2020.[45] This assumption is consistent with the fact that the overall survival of patients treated with hadrontherapy, as well as other cancer therapy methods, is usually checked 5 years after the treatment to assess the overall effectiveness. This means that in 2020 first consolidated results on effectiveness of the initial experimentations will be available. Moreover, the peack in 2020 is justified by the fact that in 2017 the research line will become operational. It is then expected that after the peack in 2020, L0 papers will be produced for the whole duration of the CNAO operations and will continue to be generated for the following ten years. According to a prudent approach, no other peaks are expected. However, in an optimistic scenario it is reasonable to predict a second peack in 2023 since the overall survival of patients affected by cancer is usually checked again 10 years after the treatment.

Papers of level 1 are expected to be generated following the shape of the papers L0 with five years of delay. Accordingly, the production of L1 papers has a peack in 2025 and then in continues over a longer period with respect to papers L0. The forecasts of L1 stop at 2055. Projections of L1 have been estimated by assuming an average number of citations to papers L0. Specifically, a citation factor with a normal probability distribution with a standard deviation of 0.3 around the mean values of 1 and 2 has been used, respectively, until and after 2013 according to the average number of citations recorded for papers so far produced by CNAO scientists and collaborators. The reason for using a greater citation factor from 2014 onwards means assuming that future papers L0 will be on average cited twice than those produced during the construction and the experimental phase.

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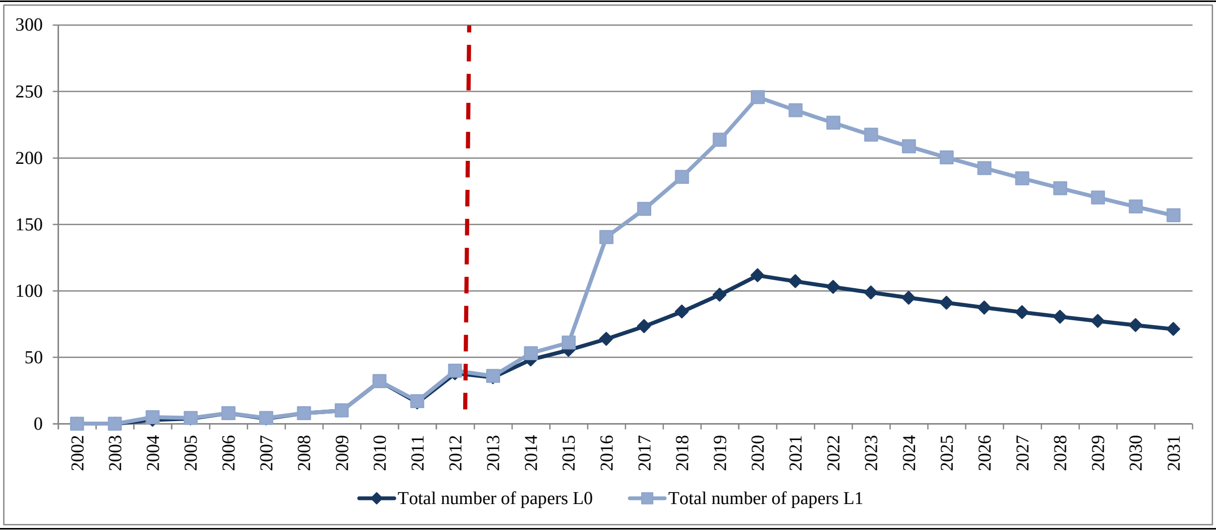
[40]It is the official journal of the Particle Therapy Cooperative Group. It aims to disseminate peer-reviewed information regarding particle therapy as well as to become the preferred location for publication of all types of information regarding particle therapy, enhance the quality of particle therapy publications, and facilitate career development of young particle therapy investigators.
[41]http://inspirehep.net/
[42]http://www.ncbi.nlm.nih.gov/pubmed
[43] http://wokinfo.com/
[44]Particle Therapy Co-Operative Group, http://www.ptcog.ch/
[45] In order to take into account the uncertainty associated with this projection a uniform probability distribution (with a ±5% variation around the baseline projected values) has been considered.

Figure 4 Trend of L0 and L1 papers



Source: Authors

Turning to the valuation of knowledge output some considerations about its shadow price of should be made. As outlined in Florio and Sirtori (2014), what is peculiar in science is that the demand for the knowledge output production function of a research facility is driven by scientists in a given field who are often at the same time users and producers of knowledge. This holds true also for CNAO, where the same scientific community involved in the design and construction of the facility is currently involved in its operation, interpretation of the evidence produced and scientific discussion. The fact that scientists are also the producers of knowledge, means that when they spend some time on a research project, they have an opportunity cost, which is the fact that they do not work on an alternative project. If this opportunity cost is assumed equal to the average scientist's hourly compensation, then a reasonable proxy of the value of scientific output is its marginal production cost. This would be the time spent by scientists to make research and produce a paper, a preprint or other knowledge outputs, valued at appropriate shadow wages. Following this approach, it can be observed that the salaries paid to CNAO scientists enter equation (1) both on the benefit, side since they can be used as a proxy of the value of scientific outputs, and on the cost side since they are a cost for the Centre. This means that CNAO scientific personnel and collaborators partially cancel out with the value of papers L0.

However, having included the salaries of CNAO scientists on the cost side, there is need to account for the value of L0 papers on the benefit side, in this way and according to the theoretical framework the two items would cancel out with each other. Under some assumptions on the average productivity of scientists and the average number of references contained in a paper and their respective probability distributions, the unit production cost/value of L0 and L1 papers is estimated to be approximately 275 and 265 EUR, respectively. Conversely, following a prudential approach, the production value of paper L2 and of those of the subsequent levels have not been estimated. Indeed, being these papers more distant to the stream of papers L0, it is more difficult to attribute their value to their original inputs.

Specifically, the scientists' productivity depends on the share of time actually devoted to research rather than other non-scientific activities and the average number of outputs produced every year to which the author has actually contributed with some time and effort. The share of time devoted to research is assumed to follow a triangular distribution with a modal value of 30% for insiders and 80% for outsiders.[46] Similarly, it is assumed that the average number of outputs takes a normal distribution with a standard deviation of 0.3 around the mean value of 2 papers per year for insiders and 5 papers

[46] The lower bound of the distribution is 20% and the upper bound is 40% for insiders. 60% and 90% are instead the parameters used for outsiders.

per year for outsiders. As for the average number of reference contained in a paper, a review of existing papers in the particle therapy field shows that the number of references is generally around 30. In the analysis, therefore it is assumed for this variable a normal probability distribution with a standard deviation of 0.5 around the mean value of 30.

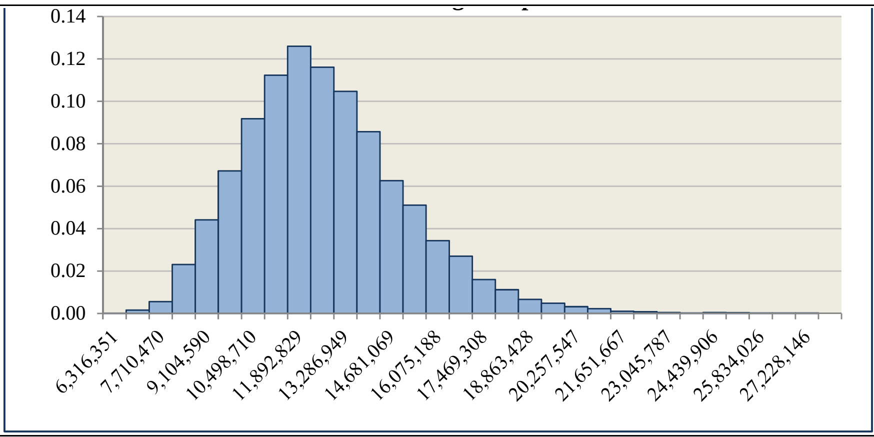
According to Florio and Sirtori (2014), the total value of knowledge is not only made by the social value of producing new information *per se* but it also comprises the social value attributed to the degree of influence of that piece of knowledge on the scientific community. While the former is captured by the number of papers written and valued through the marginal production cost, the latter is reflected in the number of people that would read the paper and decide to cite it. In particular, the use of citations is an imperfect but widely accepted approach (Hagström, 1965; de Solla Price, 1970) to measure the significance of the social recognition that the scientific community acknowledges to a paper. Following this approach the social value attributed to the degree of influence of knowledge outputs on the scientific community has been estimated.

By analogy with the value of paper production, the shadow price of citations could be estimated using the opportunity cost of time employed by a scientists to read and understand someone else's paper and decide to cite it. The extent of this time depends on the type of paper, its length, topic, the experience of the reading scientist and other variables. In the analysis one hour has been used as the average time needed to cite a paper. As a result, the average hourly gross salary of scientists is taken as an estimate of the social value of one citation.

Both the quantities and the economic value attributed to knowledge outputs considered in the analysis are uncertain. Moreover, some strong assumptions have been introduced on fundamental variables, such as the trend of increase in the CNAO scientific outputs, the average annual salary, the share of time devoted to research, the annual paper productivity, the number of references contained in L1 papers, the number of hours needed to produce citations. To account for this uncertainty, a probability distribution has been assigned to each variable and parameter instead of punctual values.[47]

The expected present value of the *S*-benefit amount to nearly EUR 12.3 million, with ranges of possible values between EUR 6.3 and 27 million.

Figure 5 Probability distribution of the knowledge outputs (Euro)



Estimated parameters of the distribution

Mean	12,328,087
Median	12,059,869
Standard deviation	2,467,813
Minimum	6,316,351
Maximum	27,228,146

Source: Authors

[47] Depending on the variables, a triangular or a normal or a trapezoidal or a rectangular probability distribution factions have been used.

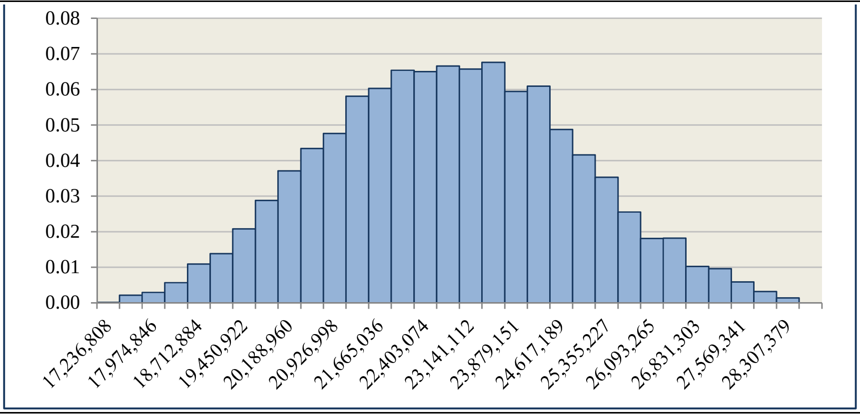
7 Technological externalities

The impact on technological progress is a societal benefit to be considered, additionally to the advancement of fundamental knowledge, when welfare effects of research infrastructures are assessed. (Kay and Llewellyn Smith, 1986; Mansfield, 1991; Technopolis Group, 2013; Del Bo, 2014). This technological progress can either be the intentional outcome of R&D collaboration programmes conducted at the research infrastructures, or the side effect of on-the-job working and learning by-doing process (Arrow, 1962). Not only technological progress can be more or less intentional, but it can also be safeguarded to different extents. While the intellectual property of new technological knowledge can be protected by means of patents, industrial designs, copyrights and trademarks, whose value can be estimated through well-established methodologies, a part of know-how generated in research infrastructures is developed through an open and collaborative approach, whose outputs are not necessarily protected and, in turn, they are more difficult to be estimated in monetary terms.

A challenge for the estimation of this benefit is that the technological progress associated with CNAO has very faint borders. As mentioned above, the research carried out in the Centre is highly collaborative in nature: since the beginning, research activity at CNAO has benefitted from an intense collaboration in particular with INFN, which led to development of shared knowledge. This makes it difficult to attribute to CNAO a specific effect of technological transfer observed in the scientific or industrial community and somehow related to the construction or operation of CNAO. In particular, the collaboration with INFN (National Institute for Nuclear Physics) and CERN, which was particularly close during the construction of CNAO, led to new technological knowledge which was not protected through intellectual property rights. As a result, when discussing the technological externalities associated to CNAO, one must bear in mind that they are strictly influenced by research activities carried out in collaboration with other research institutions, especially INFN. For this reason, a conservative approach has been preferred in order to not overestimate this benefit.

Different kind of technological spillovers are ascribable to the CNAO. First, technological spillovers might occur within the firms and laboratories along the CNAO's supply chain; a second innovation outcome that might be produced is the creation of spin-offs. In addition, it the case of CNAO a further technological spillover has been identified in the form of avoided costs for existing and future hadrontherapy centres. In total, the expected present value of CNAO technological spillovers over the 2001-2031 period amount to nearly 22.6 million EUR, of which more than a half (55%) are from avoided costs enjoyed by other hadrontherapy centres, 28% corresponding to the benefit on the supply chain and 17% related to the spin-off.

Figure 6 Probability distribution of the technological externalities (Euro)



Estimated parameters of the distribution

Mean	22,626,973
Median	22,615,159
Standard deviation	2,022,221
Minimum	17,236,808
Maximum	28,307,379

Source: Authors

7.1.1 Supply chain

Firms involved in the design and construction of the CNAO often did not have ready-made solutions to the types of problems that arose for example related to the need of increasing precision of mechanical components. According to interviews carried out with supplying companies benefitting of technological spillover, technical specifications provided by CNAO usually detailed the desired technical performance a given component or system should provide, leaving however to the supplier the challenge to provide industrial solutions to a number of technological questions. As a result, when a procurement contract was signed, an intense collaboration process between the supplier and the CNAO itself took place, aimed at effectively designing, testing and manufacturing the required product or service. These efforts gave firms the opportunity to experiment and forced them to expand beyond their current state of knowledge for producing further technological advancement to be exploited. In some cases, procurement from CNAO were the chance to buy a new machinery or to employ new staff. In other words, for high tech components or systems, procurement contracts offered to supplier firms the opportunity to increase their technological performance. According to the opinions collected on field, such new knowledge and technological skills proved to be particularly useful and appealing for the market, due to the fact that CNAO was one of the first hadrontherapy centre developed in Europe and recognised as the frontiers in that scientific field. In a number of cases, working for CNAO had a labelling effect and eventually lead to opening new markets, increase turnover and employment.

While a vast literature analysing the relationship between academic research and industrial innovation activity exists[48], the empirical literature focusing on the technological spillovers of research infrastructures is less extended. The first studies were drafted in the Seventies by NASA in the USA and CERN in Europe. In most of the latter, the economic benefits from CERN procurements have been quantified and analysed (Schmied, 1975; Bianchi-Streit *et al*., 1984; Nordberg, 1997). Specifically, in those studies the economic benefit of technology transfer is defined as the sum of the increase of turnover and saving in production cost generated by, but independent from, the procurement contracts. Other studies have instead looked at the impact of CERN contracts in terms of competence development in SMEs (Autio *et al*., 1996; Hähnle, 1997; Fessia, 2001). However, they have made little contribution in terms of attempting to quantify what those learning benefits are.

In recent years, similar studies have been carried out by the National Institute for Nuclear Physics. The Centre, as many other fundamental research institutes, requires advanced technologies that often are not part of the industrial know-how and which ask for innovative solutions. The search of such solutions provides continuos occasions of knowledge and technology transfer to the industries collaborating with INFN. In order to investigate the impact of INFN research activity on Italian industry, two types of analyses have been carried out in the past years. On one hand, a micro-level and semi-quantitative analysis of the impact of INFN on the capabilities gained by their supplier companies have been performed. On the other hand, a macro-economic analysis, based on an Input/Output Model, giving information on the impact of INFN activities on Industry in terms of increase of internal production and employment have been realised. The latter suggests that in the period 1998-2005 one Euro spent by INFN in the industrial system, would produce on average 1.79 Euro in the form of value of products (Salina, 2006). If only tech-edge orders defined as commissions and orders involving the product development are considered[49], the impact factor becomes 2 and 2.7, respectively.

A similar investigation had been performed by Schmied (1975) and Bianchi-Streit *et al.* (1984) which analysed the supply chain of CERN respectively in the periods 1955-1978 and 1973-1982. The former study suggests that the 'economic utility' ratio was in the range 1.4 and 4.2 with an average of 3. This figure would indicate that for every Euro spent by CERN in a high-tech contract, a company receives around 3 Euro in the form of increased turnover or cost savings. Improving the sampling and extrapolation methods, Bianchi-Streit *et al.* (*ibidem*) obtained the same average utility/sales ratio. Other studies (mentioned by Autio *et al.*, 2003) provide 'economic utility' ratios of 2.7 in the case of the European Space Agency, and between 1.2 and 1.6 for Big Science centres. However, the calculations behind these ratios seem to implicitly assume that the value of the externality can be

[48] See for instance Jaffe (1989), Acs *et al.* (1992) Feldman and Florida (1994) Bacchiocchi and Montobbio (2009).
[49] In other words, the supply of both low- and high-tech on the catalogueproducts are excluded.

computed simply as increased sales and decreased costs. Conversely to this approach and in line with Florio and Sirtori (2014), the change of *net* output (i.e. profit) at shadow prices needs to be considers.

Being j the number of companies benefitting from technological spillovers over time t, Π_{jt}their incremental profits at shadow prices directly imputable to the spillover effect, and s_t the discount factor, the present value of technological externalities is expressed as:

$$T = \sum_{j=1}^{J} \sum_{t=0}^{\mathcal{T}} s_t \cdot \Pi_{jt}. \quad (5)$$

The profit has to be derived as the difference between the firms' total income or cash inflow and operating costs, all valued at shadow prices. However, the causal link between the activities carried out for the CNAO and profits due to those specific activities is not obvious. Not all procurement contracts are likely to generate technological externalities. Orders regarding off-the-catalogue products are items produced for the market and which do not need substantial adaptation for being used by CNAO. As such, they do not entail any spillover effect. On the other hand, learning benefits are expected to occur when the procurement contract is for the provision of products which satisfy very specific technical requirements, duly customized to be fitting for the CNAO purpose. According to this segmentation of procurement contracts, ten firms involved in the provision of the items listed in the following table have been identified as potentially beneficiaries of a sort of technological and knowledge transfer.

On the basis of data collected during interviews, the incremental profit registered on average by the selected supplier firms can be approximated by a triangular probability distribution ranging from 1% to 10% with a modal value of 7%. A benchmark analysis of the average EBITDA margin associated to the considered companies, carried out using data gathered from the ORBIS database of world companies' balance sheets, confirms that a baseline value of 7% is reliable.

Table 9 Category of items potentially suitable for enabling technological and knowledge transfer

Items	Technological transfer to be used in a similar field	Technological transfer which can be applied in different fields
Synchrotron feeder	Yes	Yes
Conventional magnets	Yes	No
Control system	Yes	Yes
OIS	Yes	No
Vacuum system	Yes	Yes
Special feeder	Yes	No
Special magnets	Yes	No
Security systems	Yes	Yes

Source: Own elaboration based on data provided by CNAO staff

The total volume of CNAO external procurement associated with the firms potentially benefitting of knowledge transfer amounts to 25.2 million EUR (2013 constant prices). In line with the previously mentioned literature, the analysis adopts an average utility/sales ratio with a uniform probability distribution ranging from 2 to 4. By multiplying the utility/sales ratio for the total yearly procurement volume, an estimate of suppliers' turnover by year is obtained.The economic benefit is however expressed as the profit gained by companies which have enjoyed technological and knowledge transfer. Therefore, by multiplying the average profit margin to the increased annual turnover, the technological transfer benefit to suppliers is estimated. The discounted sum of benefit amounts to 8.5 million EUR in the baseline case.

7.1.2 Spin-off

An additional innovation outcome that has been produced thanks to the construction of CNAO is the creation of a spinoff aimed at commercialising the facility's research breakthroughs. Specifically, De.Tec.Tor. S.r.l. was founded in 2009 as a Turin University and Italian Institute of Nuclear Physics spin-off company to develop particle detectors for hadron-therapy centres. The spin-off is ascribable to CNAO since its creation was particularly linked to the chance of collaborating for the development of the CNAO's dose delivery system and the commissioning of the Centre, as confirmed by the one of the company's founders. Currently, it is a small company that designs, customizes and manufactures high precision particle detectors for on-line beam monitoring and daily quality assurance in advanced radiation therapy. In particular, it has recently been involved in the provision of services and hardware to the Med Austron hadrontherapy centre[50]built in collaboration, among others, with CNAO and which is currently under the commissioning phase.

In the literature of project appraisals, the economic benefit arising from the creation of new business units has often been valuedby looking at the economic value of the jobs created. This approach is not consistent with the CBA theoretical foundations. According to the methodological framework the economic value of a spin-off should be valued as the expected shadow profit gained by the enterprise during its lifetime, as compared to the counterfactual situation. In other words, the economic benefit associated with the creation of a spin-off company created to commercialise a technology associated with a research infrastructure is reflected in the cumulative profit made by the company during its entire lifecycle.[51]

In line with the stated approach an *ex-ante* estimate of the benefit should be based on the expected value of annual profits earned by spin-offs and the average lifetime of spin-offs in the considered country and sector.

Since the yearly profits recorded by De.Tec.Tor.S.r.l.were available from 2010 to 2014, they have been therefore plugged in the calculation. As for the future yearly profits, some assumptions have been made in order to evaluate the benefit. Specifically, for 2015 the profit estimated by the company has been used. From 2016 to 2020 a share of the profit estimated for 2015 has been considered[52]. This means that the time period for which the profit gained byDe.Tec.Tor.S.r.l.are ascribable to CNAO is 11 years. After this date, it is assumed that the activity of the company will be no longer linked with the technology associated to CNAO. Based on the mentioned assumptions, the discounted sum of benefit amounts to nearly 1 million EUR in the baseline case.

7.1.3 Avoided costs for Hadrontherapy centres

The construction of CNAO involved a major technological and scientific effort spanning over a long time period and involving more than a hundred and thirty private companies. The created knowledge, which involved not only technological development but also a demanding clinical trial and experimental phase, is potentially immediately useful for similar centres in the design and construction phase worldwide. This knowledge currently is owned by CNAO and can be transferred to other centres through collaboration and contracting relations. According to interviews, a number of delegations from other centres have been visiting CNAO to collect information relevant for their activities and in some cases network and collaborations are ongoing with some of them on a more stable basis. This paves the way for the direct exploitation of the knowledge developed and tested at CNAO by other centres worldwide, which would translate in avoided costs to undertake own tests and experimentations in their centres. This possibility did already materialise in the case of the MedAustron centre[53] currently under construction in Austria. The centre purchased from CNAO engineering design at a cost of approximately 8 million EUR which, according to interviews, ensured

[50] MedAustron, a center for Ion Therapy and research is located in Wiener Neustadt in Lower Austria, about 50 kilometers south of Vienna.

[51]Provided that for the entire lifecycle the activity of the spin-off is ascribable to the technology associated with the research infrastructure. Otherwise an apportionment is required.

[52] A share (ranging from 60% to 80% with a uniform probability distribution) of the profit recorded in 2015 has been considered instead of the entire future yearly profits from 2016 onwards since the activity of De.Tec.Tor.S.r.l. will progressively detach from the technology endowment gained during the collaboration with CNAO.

[53] http://www.medaustron.at/.

a cost saving of approximately 14 million EUR. This value has been included in the analysis as a direct benefit of CNAO. However, in order to take into account the uncertainty associated to this value mainly due to the difficulties of estimating the share of cost saving strictly ascribable to CNAO without including those ascribable to INFN and CERN, which collaborated in the project design, a triangular probability distribution with a minimum value of 10.8 million, a maximum value of 18 million and a mode of 14 million has been used in the analysis.

In the future it is most likely that such activity will continue and possibly improve, and the CNAO is currently considering the possibility to set up a new dedicated plant engineering company with the aim of developing the commercialisation of the design, construction, contracting and licencing of hadrontherapy facilities. Indeed, proposals collaboration in feasibility evaluation, initial design, realization of specific components have already been received from different countries, such as Croatia, China, United States and Corea. This aspect on future benefits has not yet been included in the analysis, but will be further explored for a fine tuning of the results..

8 Human capital formation

Being an applied research infrastructure where an experimental health therapy is performed, the CNAO attracts students at the end of their course of study as well as junior researchers at the beginning of their work career. Most of them, even those coming to the RI for a short period, can benefit from the development of their skills, ranging from technical and scientific abilities to personal ones, which presumably will help them achieve higher salaries over the rest of the career as compared to other young who do not spend a period at CNAO. Similarly, some skills can also be acquired by scientists, engineers and technical staff working at the CNAO. When they leave the Centre, the increase of earnings they would get in performing another job compared to what they would have get without their experience at the CNAO is a further positive externality of the infrastructure.

According to Florio and Sirtori (2014), and following the standard CBA framework for education programmes, the present value of human capital accumulation benefits produced by the research infrastructure can then be defined as the sum of the increasing earnings or income, I, gained by RI's students and former employees, commonly indexed by z, since the moment (at time φ) they leave the project.

$$H = \sum_{z=1}^{Z} \sum_{t=\varphi}^{\mathcal{T}} s_t \cdot I_{zt}. \quad (6)$$

At CNAO, the human capital formation benefit is expected for the following categories of people[54]:

- University Students, staying at CNAO for approximately 9 month during their master degree or first level master and working on CNAO-related activities for their thesis;
- Researchers, remaining at CNAO up to 1 year, and who could be distinguished among fellows and doctoral students;
- Interns, staying at CNAO for approximately 5 months for a stage, a training course or a specialization course;
- Technical Medical Radiology Volunteers, remaining at CNAO for 3 months. After this period, they are usually employed by CNAO.

The number of persons belonging to the four mentioned categories arriving every year at CNAO has been retrieved from CNAO Personnel Statistics reports, available from 2008 to 2013[55]. Since the time horizon of our analysis goes from 2008 to 2031, some assumptions for the incremental number of persons had to be made for the period 2014-2031. For caution, it was assumed that the number of

[54] Human capital formation is, so far, expected only for students and young workers.
[55] From 2001 to 2008, no students/researchers/interns/volunteers passed through CNAO.

incoming university students/researchers/interns/volunteers after 2013 assumes a normal distribution with standard deviation of 0.3 around the mean represented by 2013 value.

The following table presents the total number of university students/researchers/interns/volunteers carrying out a training period at CNAO and considered in the baseline scenario.

Table 10 Summary table of fellows and students at CERN

Variable	Number	Average staying at CNAO
Total university students	257	9 months
Total Researchers (fellows & doctoral students)	46	1 year
Total Interns	85	5 months
Total TMR Volunteers	119	3 months
Total	**507**	

Source: Authors

Turning to the estimation of the benefit, this would imply tracking careers of cohorts of students in the long run and matching data on careers and estimating the percentage increase in their salary thanks to the experience at CNAO. Based on interviews, the professional sectors where CNAO former students/young researchers are expected to find a job have been identified. These are: other hadrontherapy facilities, research centres, academia, hospital, industry, and other sectors[56]. Additionally, the share of students who find a job in one of the six mentioned sectors has been hypothesised, as presented in the following table.

Table 11 Distribution of CNAO students by professional sector

Sector	Researchers (fellows & doctoral students)	University Students	Interns	Volunteers
CNAO	0%	0%	5%	90%
Other hadrontherapy facilities	10%	10%	10%	5%
Research centres	40%	20%	30%	0%
Academia	40%	10%	30%	0%
Hospital	0%	20%	10%	5%
Industry	5%	20%	5%	0%
Others	5%	20%	10%	0%
Total	**100%**	**100%**	**100%**	**100%**

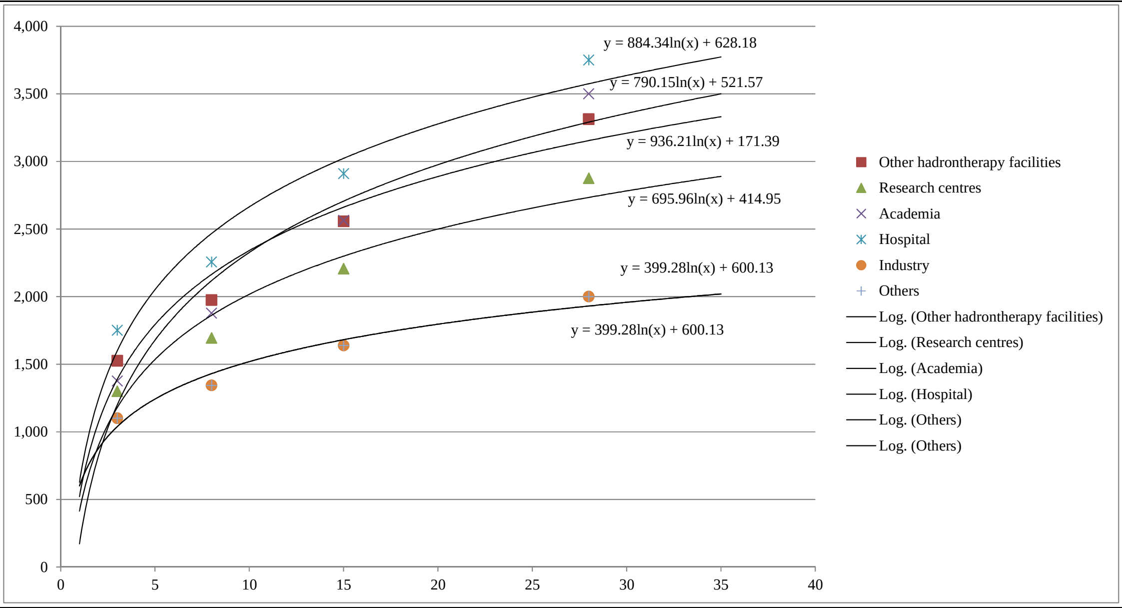
Source: Authors own assumptions.

The average salary for each of these professions, at four different career levels, has been retrieved from Istat databases.[57] Using a logarithmic function, a continuous salary curve has been estimated for each professional sector (see figure below). This process allowed to obtain the average incremental salary by year of career.

[56]This is a residual category.

[57] The salary referred to workers in other hadron therapy facilities has been assumed equal to the average salary paid at CNAO which is approximately an average among the average salaries paid in Italy to the following categories: doctors, researchers and technicians.

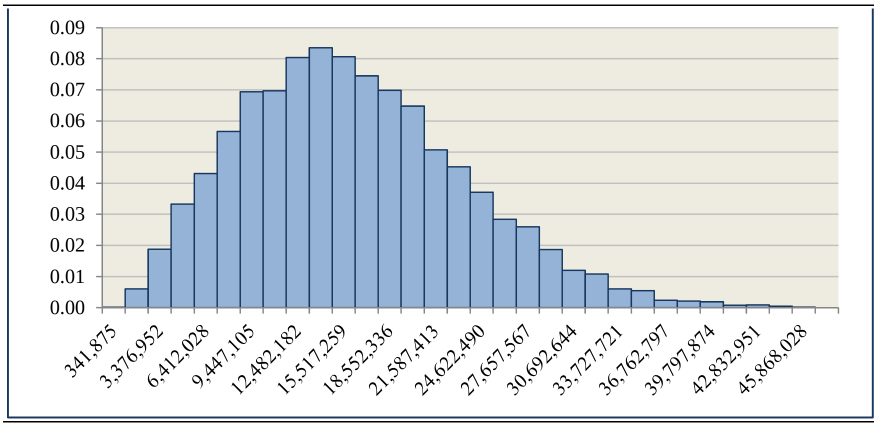
Figure 7 Curve of incremental salary by professional sector



Source: Own elaboration based on Istat salary figures.

Concerning the incremental annual salary earned by former CNAO students/researchers, it has been estimating that the salary bonus for having spent a training period at the CNAO can range from 1% to 10% with a triangle probability distribution with mode value of 5%[58]. Based on this range of variation and making the following two assumptions: 1) CNAO students/researchers enter the labour market immediately after their experience at the CNAO; and 2) the incremental salary benefit is spread over their entire work career, lasting 40 years[59], the expected present value of the benefit for human capital formation is nearly EUR 15.4 million.

Figure 8 Probability distribution of the human capital formation (Euro)



Estimated parameters of the distribution

Mean	15,440,196
Median	14,725,106
Standard deviation	7,364,337
Minimum	341,875
Maximum	45,868,028

Source: Authors

58 For simplicity, the same bonus is applied to all professional careers and all career levels.

59This means that the benefit for the cohort of student leaving the CNAO in 2031 spans until 2070.Benefits occurring beyond the last year of CBA but originating from human capital formation activities occurred up to 2031 need to be included in the calculus of the CNAO benefit.

9 Outreach and cultural impact

Among CNAO missions, besides patients' cure, there is also education to research and innovation, as an effective tool to raise young persons' interest in their future professions. According to this mission, since it become operational in 2011, CNAO has organized free guided tours for students from high schools, universities, research institutes and scientific organizations. Also, in order to promote the interaction of the Centre with society, the CNAO is engaged in organising free visits for general public. As a result, the Centre is among other a destination of the so called “science tourism”.

Besides tours and open days, in principle, other vehicles to disseminate culture on science in general and research in hadrontherapy in particular exist. Typical means of communication include lectures and seminars for a wide range of public, news on TV and radio, newspapers, websites as well as social media. However, in the analysis of CNAO outreach benefit, it was decided to focus on the benefit referred to personal visits only, which account for the largest part of the CNAO dissemination activity. Data and information have been collected through personal interviews and email exchange with CNAO Communication office.

Since the intended beneficiaries of outreach activities is the general public, with particularly emphasis on young and students, in a sense CNAO does not differ much from a museum attracting every year a number of people as tourists. There are standard CBA approaches to evaluate cultural tourism to museums or other recreational activities, like visiting a natural park. Florio and Sirtori (2014) suggest to exploit these methods for scientific tourism as well. These approaches usually rely on the estimation of the willingness to pay, W, of the general public by type of beneficiaries ($g = 1, \dots G$) for visiting the research infrastructure. Hence, we can express the benefit of outreach activities as follows:

$$C = \sum_{g=1}^{G} \sum_{t=1}^{\mathcal{T}} s_t \cdot W_{gt}. \qquad (7)$$

The travel cost method is a well-established approach for valuing the willingness to pay of people for a desirable good, in this case a visit to the CNAO.[60] It consists in evaluating a good through the full travel cost incurred in its consumption, including the cost of trips (fuel, train or airplane ticket, etc.), the opportunity cost of time spent in travelling, the cost of accommodation, food, and so on. Given the number of visitors to the site in a given time period and the marginal economic cost of a trip, the demand curve can be derived and the willingness to pay for a visit estimated[61]. In particular, the travel cost method proposed by Jack Clawson and Marion Knetsch in 1966[62] has been followed.

A first step in the application of the travel cost method consists in quantifying and estimating the number of visitors. As for the period 2011-2014, the historical number of visitors to CNAO guided tours were made available by the CNAO communication office. Considering that free tours take place four times per year when the accelerator is turned down for regular maintenance[63], there are a maximum of 8 days per years available for organising guided tours, meaning a maximum number of 1800 visitors per year. This figure has been adopted as the number of visitors from 2014 onwards.

A second step consist in defining origin-destination matrixes. Again, thanks to historical data of visits, five possible areas of origin, located at increasing distances from Pavia, have been identified (see table below).

[60] See Florio (2014) for a review of methods to estimate the willingness to pay for a good.

[61] The travel cost method however is affected by a limitation that should be carefully dealt with. It has to do with the apportionment issue arising whenever it is reasonable to assume that a trip is made for different reasons (multi-purpose trip) and not for visiting a specific RI. Actually it could be arduous to disentangle the willingness to pay of visitors for a given infrastructure when more than one attraction are located in the same site or in the same area. However, in the case of CNAO an apportionment assumption seems not necessary since its visitors are purposely CNAO specific.

[62]It still the main reference for the estimation of willingness to pay for visiting recreational sites.

[63] Each regular maintenance period lasts four day. However, only two days can be used for organizing tours.

Table 12 Origin of visitors

# Zone	Zone description	% of visitors
Zone 1	area within a radius distance below 20 km from Pavia	28.6
Zone 2	area within a radius distance between 20 and 500 km from Pavia	67.8
Zone 3	area within a radius distance between 500 and 3,000 km from Pavia	1.2
Zone 4	area within a radius distance between 3,000 and 7,000 km from Pavia	0.4
Zone 5	area beyond a radius distance of 7,000 km from Pavia	2.00

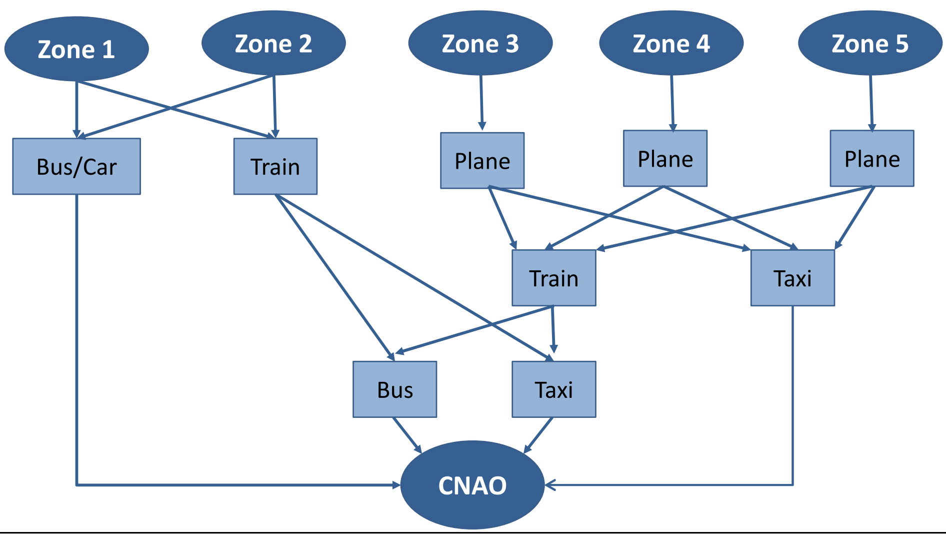
Source: CNAO historical data of visits.

Once the travel zone has been identified, the average travel cost associated to each of them has been estimated. Specifically, three are the items of cost considered: the cost of lunches/accommodation, the cost of the trip and the opportunity cost of time spent in travelling.

As far as lunches/accommodation cost are considered, a subdivision between visitors remaining for one day only and those staying over one night have been made according to historical data. Specifically, a percentage of almost 97% of visitors is supposed to remain for one day only. Considering that, all CNAO guided tours are for free, the cost of their stay includes only one lunch, ranging from 8 to 12 EUR[64]. The remaining nearly 3% of visitors, which includes those travelling from more than 500 km to come to CNAO, are assumed to stay one night at the cost ranging from 60 to 80 EUR[65]. Also, the cost of two lunches in Pavia amounting to a total cost ranging from 40 to 60 EUR[66] per person is included in their cost of stay.

Depending on the origin zone, different transport modes have been taken into account when estimating the cost of trips for visitors to CNAO. Specifically: plane, train, bus, car and taxi. Also, according to the origin zone, the total travel length has been divided into one or more sections corresponding to the use of different transport modes. The result of this segmentation process is a number of combinations between origin and transport modes, which is outlined in the figure below.

Figure 9 Outline of transport modes by origins and travel sections



Source: Authors. Note: Obviously, the number of travel section depends on the distance between the origin point and the CNAO.

[64] Following a triangular probability distribution with modal value of 10 Euros. The range of variation is based on authors' own experience.
[65] Following a triangular probability distribution with modal value of 70 Euros. The range of variation is based on data available on www.Booking.com.
[66] Following a triangular probability distribution with modal value of 50 Euros.

Considering the first section, depending on the origin zone, visitors may come by train, plane or car/bus (see table below). Shares of visitors by transport mode are own assumptions partially based on historical data. For example, car or bus may be used by people coming from shorter distance, while people coming from longer distance are more likely to prefer the train or plane. The average cost and travel time has been retrieved from different travel websites. Specifically, the average travel cost and time for Zone 1 is estimated as the average travel cost from Pavia city centre to CNAO; the average travel cost and time from Turin and from Moscoware considered for zone 2 and 3, respectively; the average travel cost and time fromNew York and Tokio are considered for zone 4 and 5, respectively. Cities were selected among those placed in countries from which significant shares of visitors usually come.

Table 13 Average travel cost and shares of use by transport mode – first section

	Option 1: TRAIN			**Option 2: PLANE**			**Option 3: BUS/CAR**		
Origin-Destination (first section)	cost (EUR) A/R	time A/R (h)	SHARE by train	cost (EUR) A/R	time A/R (h)	SHARE by plane	cost (EUR) A/R	time A/R (h)	SHARE by car
Zone 1 (0-20 km)	-	-	-	-	-	-	2.50	0.5	100%
Zone 2 (20-500 km)	62.00	2.9	30%	-	-	-	28.33	4.0	70%
Zone 3 (500-3000 km)	-	-	-	389	7.8	100%	-	-	-
Zone 4 (3000-7000 km)	-	-	-	460	18.0	100%	-	-	-
Zone 5 (Over 7000 km)	-	-	-	1,200	25	100%	-	-	-

Source: Different travel websites for cost and time of train, plane and road options; own assumption for share of visitors by transport mode.

As for the other travel sections, the following assumption have been considered:

- visitors arriving to the Milan airport, i.e. those arriving from zone 3, 4 and 5 and travelling with plane, may continue their travel to CNAO either by taxi or by train and in this second case, once arrived at the Pavia train station can reach CNAO either by taxi or by bus;
- those coming by train and arriving at the Pavia train station, i.e. those from zone 2, can reach CNAO either by taxi or by bus.

Once the possible combinations of transport modes for each travel section have been defined, the share of passengers per transport mode needs to be established. In other words, the joint probabilities between the combination of transport modes and the share of passengers need to be estimated.

Table 14 Share of passengers per transport mode (joint probabilities)

SHARE OF PASSENGERS PER TRANSPORT MODE (joint probabilities)	**Option train + bus**	**Option train + taxi**	**Option Plane + taxi**	**Option plane + shuttle + train + bus**	**Option plane + shuttle + train + taxi**	**Option bus/car**
Zone 1 (0-20 km)	-	-	-	-	-	100.00%
Zone 2 (20-500 km)	24.00%	6.00%	-	-	-	70.00%
Zone 3 (500-3000 km)	-	-	10.00%	70.00%	20.00%	-
Zone 4 (3000-7000 km)	-	-	10.00%	70.00%	20.00%	-
Zone 5 (over 7000 km)	-	-	10.00%	70.00%	20.00%	-

Source: Own assumptions based on historical data on visitors' origins.

The last cost factor to be considered is the opportunity cost of time spent in travelling. According to the literature, the time spent in work- and leisure-trips should be valued in a slightly different way. The idea behind this approach is that time spent for work-related trips are a cost to the employer, who could have used the employee in an alternative productive way. Therefore, the value of time can be estimated using the the adjusted gross hourly labour cost. Instead, for non-work related trips the time spent should be valued at consumers' willingness-to-pay, which measures how much people value their leisure time. In this regard, HEATCO study (HEATCO, 2002), provides a framework with reference values for the EU-25[67].

Based on the HEATCO travel time values related to working or leisure trips, the opportunity cost of time for different categories of visitors has been estimated. Specifically, if visitors are general public or high-school and university students the value of time for leisure has been used. Instead, for visitors coming from other research centers the value of working time has been used. The estimated 2013 adjusted values of time are presented in the following table.[68] In the risk analysis, it was assumed that these values take a normal probability distribution with a standard deviation of 0.3 with respect to the mean values presented in the table below.

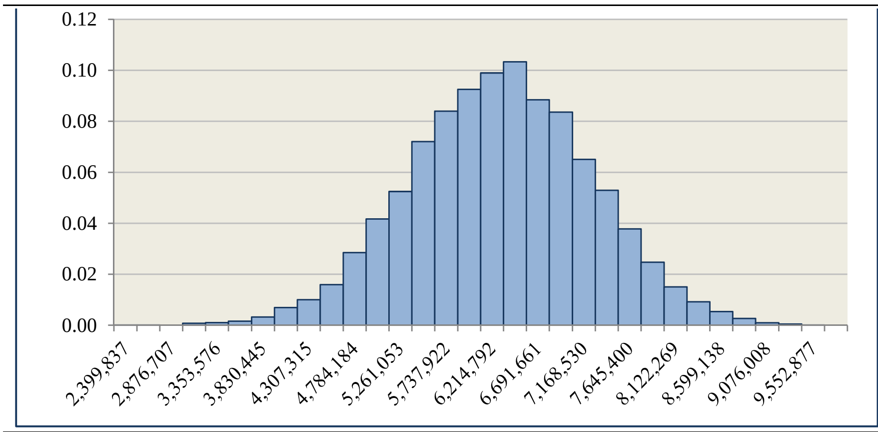
Table 15 Estimated values of time (per passenger hour). 2013 adjusted values of time (Euro)

	Air	Bus	Car, Train
Working time	35.8	20.9	26.0
Non-working time; short distance	13.81	6.66	9.26
Non-working time; long distance	17.76	8.55	11.90

Source: Own calculation based on HEATCO data.

The total expected present value of the cultural outreach amounts to nearly EUR 6.2 million with ranges of possible values between nearly EUR 2.4 and 9.6 million.

Figure 10 Probability distribution of the cultural outreach (Euro)



Estimated parameters of the distribution

Mean	6,183,686
Median	6,188,477
Standard deviation	942,021
Minimum	2,399,837
Maximum	9,552,877

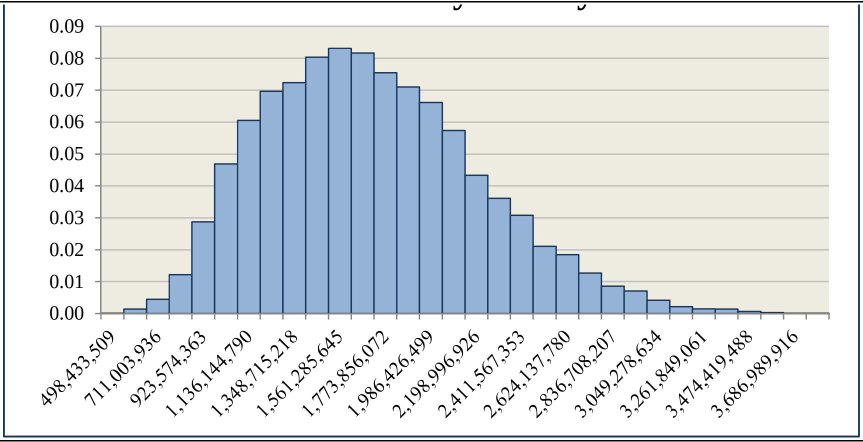
Source: Authors

10. The CNAO expected net present value

The present paper has tested the use of a pioneering CBA framework for the assessment of the net socio-economic impact of an advanced research facility for hadrontherapy. The results of the analysis (see Figure below) show that over a time horizon of 30 years and under a number of rather conservative assumptions on forecasts, the Centre is expected to provide net benefits amounting to approximately 1.6 billion discounted EUR. In addition, risk analysis shows that the project is affected by a low level of risk, considering that there is nil probability for the net present value to be negative.

[67] HEATCO values are taken as reference also by the European Commission's Guide to Cost-Benefit Analysis of investment projects.
[68] Using the European average GDP growth, the average EU HEATCO values of time have been adjusted to the year 2013.

Figure 11 Economic Expected Net Present Value (Euro)



Estimated parameters of the distribution

Mean	1,658,358,087
Median	1,615,046,849
Standard deviation	499,225,618
Minimum	498,433,509
Maximum	3,686,989,916

Source: Authors

Not surprisingly the composition of benefits is heavily affected by the category of benefits *A*, relating to the services provided by the infrastructure to its users, in particular, to patients. Indeed, clinical treatment provided in CNAO are the application of knowledge and technologies developed by the particle physics scientific community as well as of the advanced research activities which is continuously carried out in the Centre.

Such positive results are mainly explained by the fact that the assumptions made for the estimation of applied research benefits on patients are underpinned by a strong and well accepted scientific case about the effectiveness of hadrontherapy for tumor treatment as compared to traditional therapy. It is therefore not surprising that most of the benefits are coming from the health improvements of patients due to the provision of carbon ion therapy treatments, which qualifies as the direct application of research results to external users of the facility. A minor but still relevant share of benefits is the one attributable to proton therapy. Additional benefits are those related to the services provided to the external users for research purposes (revenues from selling the beam line), the creation of new scientific knowledge, technological spillovers and human capital formation.

The results point to a strong economic case to support CNAO considering the significant contribution to satisfy an increasing demand of tumor clinical treatment for specific categories of patients. The analysis also suggests that benefits are maximised as much as the selection of patients is made considering the marginal effect of the therapy provided in CNAO as compared to conventional treatment. It is also worth noting that from a social welfare point of view benefits from the carbon ion therapy alone would overweight the total net present value of costs and therefore provide a proper justification for CNAO.

Overall the analysis shows that the CBA proved to be a promising tool for the provision of a systematic information basis to support decision making. In particular, it allows for clearly identifying and as far as possible quantifying and translating into economic values aspects of the activities of applied scientific research which do not usually undergo an in-depth economic scrutiny. Considerations other than socio-economic welfare are also relevant when deciding about supporting a research facility and are not explicitly treated with CBA but can be somehow reflected in its key assumption. For example, the scientific case of the CNAO is somehow reflected in the assumptions on the effectiveness of the treatment against the counterfactual of conventional therapies. Again, the so-called 'business case' can somehow be included in the financial analysis which has not been treated here but according to some traditional CBA framework (see for example Florio, 2014) is the starting point of economic analysis and could somehow deal with aspects of financial sustainability and profitability from the point of view of different funding sources.

At the same time, the test of the methodological framework proved to be challenging for the well-known issue of data intensity of the analytical tool and, even more, for the specificities of the research activities carried out in the Centre. Some further research is needed in order to better capture the nature and magnitude of some of the core activities of these kinds of facilities, in particular as far as knowledge creation and technological transfer are concerned. There is in fact the impression that such benefits are underestimated in the results presented here, for a number of reasons which are however related to the specific nature of research activities carried out in the Centre.

First of all, as already pointed out, the scientific knowledge developed in the Centre is only partially and unsystematically translated into tangible outputs suitable to be tracked with scientometric techniques. Opinions collected on field support the argument that there is an intensive informal exchange of knowledge in the field of particle therapy which is not reflected in refereed journal article but are mainly transmitted with participation in conferences and events, working groups and even bilateral meetings and visits. This is exacerbated by the rather hybrid character of the scientific communities involved in particle physics which range from Particle Physics to Accelerator technologies to Health and medical treatment with extensive cross-fertilisation among them. The accumulation of knowledge in such a small but heterogeneous community is a collaborative effort which makes it is difficult to attribute to a specific research programme or facility and it not ruled by strict intellectual property rights

The same argument applies to some extent also to the aspect of technological spillover and transfer. Interactions with industrial actors or other medical centres interested in developing the technological capacities developed thanks to the construction and operation of CNAO are normally managed in an informal and relatively open and collaborative way, as it is typical in the scientific field. While this may result in a more effective and successful way of producing and spreading the knowledge within the scientific community, it makes it more challenging to assess the marginal increase in the technological development in the community attributable to the specific research facility. To reinforce this, it is worth mentioning that within CNAO there is an increasing awareness that much of the knowledge and competences developed by either the scientific and technical staff internal to CNAO but also by external users and the wider network is huge and not sufficiently exploited. It is currently under discussion the possibility for CNAO to set up a dedicated structure to sell on the market the design, planning and experimental capacity in the hadrontherapy field developed with the construction of CNAO. If this strategy should materialise, the potential economic and financial benefit of such an operation are expected to be significant and would partly reflect the benefits which currently could not be fully captured by the analysis.

To sum up, the CBA framework proved to be a suitable and relevant framework of analysis, useful for the assessment of the infrastructure of applied research. At the same time further research would be necessary to fine tune and expand the current methodologies and techniques to track the creation and dissemination of scientific and technological knowledge within a given scientific community attributable to a specific research facility.

References

Abelson, P. (2008), *Establishing a Monetary Value for Lives Saved: Issues and Controversies*, WP 2008-02 in cost-benefit analysis, Office of Best Practice Regulation, Department of Finance and Deregulation, Sydney University.

Abelson, P. (2010), *The Value of Life and Health for Public Policy*, Macquarie University, http://www.appliedeconomics.com/au/pubs/papers/pa03_health.htm

Acs, Z.J., Audretsch, D.B., Feldman, M.P. (1992). 'Real effects of academic research: comment', *The American Economic Review*, 92 (1), 363-367.

Alberini, A. and Chiabai, A. (2007), 'Urban Environmental Health and Sensitive Populations: How Much are Italians Willing to Pay to Reduce Their Risks', *Regional Science and Urban Economics*, Vol. 37, pp. 239-258.

Alchian, A. (1963) Reliability of Progress Curves in Airframe Production, *Econometrica*, vol. 31, pp. 679-693.

Amaldi, U. and Magrin, G. (eds.)(2005) The Path to the Italian National Centre for ion therapy, Ed. MercurioS.r.l., Vercelli.

Arrow, K.J. (1962) The Economic Implications of Learning by Doing, *The Review of Economic Studies*, Vol. 29, No. 3, pp. 155-173.

Ashenfelter (2006) Measuring the value of statistical life: problems and prospects, WP 111916, NBER Working Paper series.

Autio E., Hameri AP., Nordberg M. (1996) A framework of motivations for industry–big sciencecollaboration: a case study. *Journal of Engineering and Technology Management* Vol. 13(3-4), pp. 301-314.

Autio E., Bianchi-Streit, M. and Hameri, A-P. (2003) *Technology transfer and technological learning through CERN's procurement activity*, CENR 2003-005, CERN Geneva.

Bacchiocchi, E. and Montobbio, F. (2009) Knowledge diffusion from university and public research. A comparison between US, Japan and Europe using patent citations. *The Journal of Technology Transfer*, Vol 34(2): 169-181.

Bianchi-Streit M., Blackburne N., Budde R., Reitz H., Sagnell B., Schmied H., Schorr B. (1984) Economic Utility resulting from CERN contracts (Second Utility). CERN Yellow Report CERN 84/14and 1988. Quantification of CERN's Economic Spin-off.*Czech J. Phys*. Vol. B38, pp. 23-29.

Boardman et al., (2006), *Cost-Benefit Analysis: Concept and Practice*, 3rd edn, Upper Saddle River, New Jersey: Pearson Prentice Hall

Carrazza, S. Ferrara, A. and Salini, S. (2014), 'Research infrastructures in the LHC era: a scientometric approach' paper produced in the frame of the research project "Cost Benefit Analysis in the Research, Development and Innovation Sector" part of the EIB University Sponsorship programme (EIBURS).

Carson, R.T. (2011) *Contingent Valuation. A Comprehensive Bibliography and History*, Chaltenha, (UK): Edward Elgar Publishing.

Carson, R.T. and T. Groves (2007), ‘Incentive and informational properties of preference questions’, *Environmental and Resource Economics*, Vol. 37, No. 1, pp. 181-210.

Clawson, M. and Knetsch, J.L. (1966), *Economics of outdoor recreation*, Johns Hopkins Press.

Cohen, W., and Levinthal, D. (1990) Absorptive capacity: A new perspective on learning and innovation, *Administrative Science Quarterly*, Vol. 35, No. 1, pp. 128-152.

Del Bo, C. (2014), ‘The rate of return of investment in R&D infrastructure: an overview’, paper produced in the frame of the research project “Cost/Benefit Analysis in the Research, Development and Innovation Sector”, part of the EIB University Sponsorship programme (EIBURS).

De Solla Price, D. J. (1970), ‘Citation Measures of Hard Science, Soft Science, Technology and Non Science’, in C.E. Nelson and D.K. Pollack (eds) *Communication among Scientists and Engineers*. Lexington, MA: Heah, 3-22.

Drèze J., Stern N. (1987), ‘The theory of cost-benefit analysis’, in Auerbach A.J and Feldstein M. (eds), *Handbook of public economics*, North Holland, Amsterdam, Vol. II.

Drèze J., Stern N. (1990), ‘Policy reform, shadow prices and market prices’, *Journal of Public Economics*, Vol. 42, No.1, pp. 1-45.

European Commission (1999) ExterneE Externalities of Energy, Luxembourg, European Commission DG XII.

European Commission (2014) ‘Guide to Cost-benefit Analysis of Investment Projects. Economic appraisal tool for Cohesion Policy 2014-2020’. Forthcoming.

Feldman, M.P. and Florida, R. (1994). ‘The geographic sources of innovation: technological infrastructure and product innovation in the United States’, *Annals of the Association of American Geographers*, 84, 210-229.

Fessia P. (2001) Trial study of the impact of CERN contracts on firms: the development of new productsand competences. Postgraduate Internship Report, Postgraduate program in Management Technology,EPFL-HEC Lausanne.

Florio (2014) *Applied Welfare Economics: Cost-Benefit Analysis of Projects and Policies*, London: Routledge.

Florio M., Sirtori E. (2014), ‘The Evaluation of Research Infrastructures: a Cost-Benefit Analysis Framework’, paper produced in the frame of the research project “Cost/Benefit Analysis in the Research, Development and Innovation Sector”, part of the EIB University Sponsorship programme (EIBURS).

Fokas, E., Kraft, G., An, H., Engenhart-Cabillic, R. (2009) ‘Ion beam radiobiology and cancer: time to update ourselves’, *Biochim Biophys Acta*. Vol. 1796, No. 2, pp. 216-29.

Fossati, P., Ricardi, U., Orecchia, R. (2009) Pediatric medulloblastoma: toxicity of current treatment and potential role of protontherapy. *Cancer Treat Rev*. Vol. 35, No. 1, pp. 79-96.

Fudenberg, D. and Tirole, J. (1983) Learning-by-Doing and Market Performance, *The Bell Journal of Economics*, Vol. 14, No. 2, pp. 522-530.

Hähnle M., (1997) R&D collaboration between CERN and industrial companies. Organisational andspatial aspects.Dissertation September 1997 Vienna University of Economy and BusinessAdministration.

Hagström, W. (1965) *The Scientific Community*, New York: Basic Books.

Hausman, J. A. (Ed.) (1993) *Contingent Valuation: A Critical Assessment*, North-Holland, Amsterdam.

HEATCO (2002), "Developing Harmonised European Approaches for Transport Costing and Project Assessment", Sixth Framework Programme 2002-2006.

Hicks, D. (2004) The four literatures of social science. In:Glaenzel W, Moed HF, Schmoch U (eds) *Handbook of quantitative science and technology research: the use of publication and patent statistics in studies of S&T systems*.Kluwer Academic Publishers, Dordrecht, pp. 473–496

JASPERS (2013). *Project Preparation and CBA of RDI Infrastructure Project*, Staff Working Papers, JASPERS Knowledge Economy and Energy Division.

Jongejan, R. B., Jonkman, S. N., Vrijling, J. K. (2005) Methods for the economic valuation of loss of life in *CiteSeerX.*

Johannesson, M. and Jönsson, B. (1991) Economic evaluation in health care: Is there a role for cost-benefit analysis?, *Health Policy*, Vol. 17, No. 1, pp. 1–23.

Kamada T, Tsujii H, Tsuji H, Yanagi T, Mizoe JE, Miyamoto T, Kato H, Yamada S, Morita S, Yoshikawa K, Kandatsu S, Tateishi A. (2002), 'Efficacy and Safety of Carbon Ion Radiotherapy in Bone and Soft Tissue Sarcomas', *J Clin Oncol*, Vol. 20, pp. 4466-71.

Kay, J.A., and Llewellyn Smith, C.H. (1985) 'Science Policy and Public Spending', *Fiscal Studies*, Vol. 6, No. 3, pp. 14-23.

Karnofsky D.A., Burchenal J.H. (1949) "The Clinical Evaluation of Chemotherapeutic Agents in Cancer." In MacLeod CM (Ed), *Evaluation of Chemotherapeutic Agents*. Columbia Univ Press. P. 196.

Landefeld, S. and Seskin, E. (1982) The economic Value of Life: Linking Theory to Practice, AJPH Vol. 72, No. 6.

Lederman L.M., (1984), 'The Value of Fundamental Science', *Scientific American*, Vol. Vol. 251, No.5

Loeffler J.S. and Durante, M. (2013) Charged particle therapy–optimization, challenges and future directions. *Nat Rev Clin Oncol*, Vol. 10, No.7, pp. 411–424, available at: http://dx.doi.org/10.1038/nrclinonc.2013.79

MacDonald, S.M., Sethi, R., Lavally, B., Yeap, B.Y., Marcus, K.J., Caruso, P., Pulsifer, M., Huang, Mi., Ebb, D., Tarbell, N.J. and Yock, T.I. (2012) 'Proton radiotherapy for pediatric central nervous system ependymoma: clinical outcomes for 70 patients' presented at the International Symposium on Pediatric Neuro-Oncology on June 24, 2012, in Toronto, Canada.

Mansfield, E. (1991) 'Academic Research and Industrial Innovation', *Research Policy*, Vol. 20, pp. 1-12.

Mrozek, J. R. and Taylor, L. O. (2002), What determines the value of life? a meta-analysis. *J. Pol. Anal. Manage.*, Vol. 21, pp. 253–270.

Nederhof, A.J. (2006) ‘Bibliometric monitoring of research performance in the social sciences and the humanities: a review’, *Scientometrics,* Vol. 66, pp. 81-100.

Nordberg M. (1997) Transaction costs and core competence implications of buyer-supplier linkages; thecase of CERN. *Thesis,* KatholiekeUniversiteit Brabant.

NuPECC (2013), Nuclear Physics in medicine , Chapter 1, Hadrontherapy, ESF

OECD (2010) ‘Valuing Lives Saved from Environmental, Transport and Health Policies: a Meta-Analysis of Stated Preference Studies’ in Working Party on National Environmental Policies, Paris

OECD (2012) ‘The value of Statisical Life: a Meta-Analysis’ in Working Party on National Environmental Policies, Paris

Pancotti, C., Pellegrin, J., Vignetti, S. (2014) ‘Appraisal and selection of Research Infrastructures: Approaches, methods and practical implication', paper produced in the frame of the research project “Cost/Benefit Analysis in the Research, Development and Innovation Sector”, part of the EIB University Research Sponsorship programme (EIBURS).

Pötter, R., Schmid, M., Balosso, J., Baumann, M., Combs, S. E., Debus, J., Dörr, W., Dosanjh, M., Fossati, P., Georg, D., Habrand, J-L., Mayer, R., Mock, U., Orecchia, R., Vogin, G., Wambersie, A., Schreiner, T. (2013) ‘Initiation of an International Ion Therapy Research Board’ on behalf of ULICE Workpackage 2.3 and the International Ion Therapy Research Board in *NIRS & MedAustron Joint Symposium on Carbon Ion Radiotherapy*.

Pearce, D.W, Atkinson, G. and Mourato, S. (2006) *Cost-Benefit Analysis and the Environment. Recent developments*, Paris: OECD Publishing.

Salina, G. (2006) Dalla ricerca di base al trasferimento tecnologico:impatto dell’attività scientifica dell’istituto nazionaledi fisica nucleare sull’industria italiana*, Rivista di cultura e politica scientifica,* No. 2/2006.

Schmied H. (1975) A study of economic utility resulting from CERN Contracts CERN Yellow ReportCERN 75–5 and 1977 *IEEE Trans. Eng. Mgt*. Vol. EM–24 No. 4, pp. 125–138.

Schulz-Ertner, D., Karger, C.P., Feuerhake, A.et al (2007) Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas, *Int. J. Radiat Oncol Biol Phys*, Vol. 68, pp. 449-57.

Spence, A.M. (1981) The Learning Curve and Competition*, The Bell Journal of Economics,*Vol. 12, No. 1, pp. 49-70.

Sund, B. (2010) *Economic Evaluation, value of life, stated preference methodology and determinants of risks*, Örebro University 2010.

Technopolis Group (2013). *Big Science and Innovation,* report prepared by Simmonds P., Kraemer-Mblua E., Horvath A., Stroyan J. and Zuijdam F., Unied Kingdom.

Tsujii, H., Kamada, T., Shirai, T., Noda, K., Tsuji, H., Karasawa K (Eds) (2014) *Carbon-Ion Radiotherapy Principles, Practices, and Treatment Planning*, Springer Japan.

Viscusi, W. and Aldy, J. E. (2003), ‘The value of a statistical life: a critical review of market estimates throughout the world’, *Journal of Risk and Uncertainty*, Vol. 27(1), pp. 5-76.

Vrijling, J.K., Hengel, W.V. and Houben, R.J. (1998) ‘Acceptable risk as a basis for design’. *Reliability Engineering and System Safety*, Vol. 59, pp. 141-150.

Wilson, R.R. (1946) ‘Radiological use of fast protons’, *Radiology*, vol. 47, pp. 487–491.