Cost-Benefit Analysis of applied research infrastructure. Evidence from health care.

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Abstract

The present study aims at offering empirical evidence to improve existing knowledge and theory building on research infrastructure evaluation. Through an inductive case study research strategy, an innovative cost-benefit analysis framework has been used to assess the impact of an applied research infrastructure. The case study is the National Hadrontherapy Centre for Cancer Treatment (CNAO) located in Pavia (Italy). 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 non-commercial accelerators technology and sophisticated control and dose delivery systems. The analysis shows that with a fairly high probability the Centre provides a positive 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 or they have no alternatives. 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 Cost-Benefit Analysis (CBA) 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). Evidences show that the adopted CBA framework 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, Applied Research infrastructures, Healthcare, Hadrontherapy

JEL Codes: D61, D81, I23, O32

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1 Introduction

Research development and innovation (RDI) have definitely been recognised by policy makers as fundamental drivers of economic growth (European Commission, 2014a; Krammer, 2015; OECD, 2015; Sakurai et al., 1996). Capital – intensive research projects are developing at rapid pace both in number, size and cost (ESF, 2013; OECD, 2010a; ESFRI, 2010). These investment projects include both pure research infrastructures (RI), carried out for the main purpose of increasing the understanding of fundamental scientific principles and producing new ideas, but also applied research facilities aimed at acquiring new knowledge directed to a practical purpose (e.g. creating a new compound, technology or product). Considering the public budget constraint scenario, there is a growing debate on the opportunity to invest huge public sources in such big research program and related infrastructure and on the evaluation approaches and evidence based studies available to guide policy decisions (Hallonsten et al., 2004; Salter and Martin, 2000; Science and Technology Facilities Council, 2010; SQW Consulting, 2008; Vilkkumaa et al, 2015). In the past few years, preliminary attempts have been made to provide guidelines and empirical data for consultants and public officers involved in appraising RI projects (European Commission, 2014b; JASPERS, 2013). These attempts try to improve existing methodological frameworks of the Cost-Benefit Analysis (CBA), largely adopted in public decision-making to assess investment projects, into the practice of the RDI sector. Starting from these works, Florio and Sirtori have explored and discuss the most relevant methodological issues involved in a CBA for capital- intensive RDI projects and developed a new CBA framework to evaluate the net social benefits of RIs (Florio and Sirtori, 2014). This method appears as the more complete and sound yet been developed in the existing literature for RIs evaluation. However, the application of this brand new CBA framework in this field of RIs is still limited, so "to what extent the CBA can reveal to be useful decision tool in this area is an open question" (Florio and Sirtori, 2014, p. 37).

The present study attempts to fill this gap testing the RIs' CBA framework to an applied research infrastructure aiming at offering empirical evidence to improve existing knowledge and theory building/development on RI evaluation.

Medical Sciences are a privileged field of applied research infrastructure. Based on Riportal database on RI, almost 15% of all the RIs in Europe are of this scientific domain, and within the European Strategy Forum on Research Infrastructures roadmap (ESFRI, 2010), medical sciences is the scientific domain with the major share of priority projects.

Medical science and health care sector are consolidate and still growing fields for literature and expertise on economic evaluation of new procedures, services and programs (Drummond, 2005; Drummond and McGuire, 2001; Neumann, 2005). Studies have been conducted by scholars from different fields such economists, medical researchers, clinicians with the aim to compare alternative courses of action in terms of both their costs and consequences (Drummond, 2005). Different methods have been developed to perform health care economic evaluation, each of those dealing with costs but differing in the way benefits are measured and valued. Among those, CBA, which values the benefits in monetary terms, is considered the main evaluation method and it is one of the most widespread and known to judge whether an intervention is worthwhile (Brent, 2003). Nonetheless, at this time there is scant evidence of CBA systematically performed on applied RIs in health care sector.

The paper adopts an inductive case study research strategy (Yin, 2009). The case study selected (the National Hadrontherapy Centre for Cancer Treatment - CNAO - in Pavia, Italy) is a particle accelerator specifically designed to provide oncological medical treatment and to carry out research in clinical, radiobiological and dosimetric matters. While focusing on the analysis of a specific infrastructure, the paper more generally provides useful insights to develop theory on the economic assessment of applied research infrastructure through CBA.

This paper is structured as follows. After a discussion of the main cost and benefit dimensions of Florio and Sirtori CBA framework for RI, the research methodology is presented. Then the findings are discussed and finally implications and conclusions are presented.

2 RIs cost-benefit analysis. An evaluation framework

Cost-Benefit Analysis is an analytical tool aimed at informing decision making on the economic viability of projects, programmes, policies or regulatory initiatives by i) identifying all the costs and benefits and ii) measuring them through a monetary value of the welfare change attributable to them (Boardman et al., 2010; 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).

In their recent work Florio and Sirtori (2014) have explored some of the methodological challenges involved in a CBA framework for capital-intensive research infrastructure projects. Developing Drèze and Stern’s (1987, 1990) CBA theoretical framework, the scholars propose a conceptual model based on the estimation of quantities and shadow prices of cost aggregates, and a five main categories of economic benefits:

1. Knowledge output: this relates to the production and dissemination of new knowledge in a given scientific field, and it is typically related to scientific publications;
2. Technological spillovers: 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;
3. Human capital formation: this relates to the training and educational benefits of students and professionals involved in research activities;
4. Cultural effects of the project outreach activities: 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.
5. Benefits produced by the service provided by the infrastructure to its users: these are typical and often the most relevant one of applied research facilities, e.g. effects on the health of treated patients, environmental protection services, energy efficiency, testing of materials for private companies and license deals, etc.

The conceptual model includes also a non-use (existence) value of scientific discover, which is however less relevant in the case of applied research facilities and therefore it will not be considered in the present analysis.

According to this methodological framework, a research infrastructure 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, labour cost (including scientific personnel) and labour costs of other administrative and technical staff working at the RI, other operating costs, such as materials, energy, communication, maintenance, etc., and negative externalities, like air pollution or noise during construction and operations.

3 The research method

The goal of this paper is to test the soundness and reliability of Florio and Sirtori’s CBA evaluation framework for assessing applied research infrastructure, aiming at offering empirical evidence to improve existing knowledge and theory development on RI evaluation.

Case study is a robust research strategy methodology to investigate a contemporary phenomenon in depth within a real-life context (Yin, 2009). Given the novel of theoretical contributions in this field, a qualitative research methodology based on an inductive single-case study approach was deemed the most appropriate method (Edmonson and McManus, 2007; Eisenhardt, 1989; Yin, 2009). Among the RIs in healthcare, the National Hadrontherapy Centre for Cancer Treatment (CNAO) in Pavia, Italy, has been selected.

Hadrontherapy

Hadrontherapy is the field where knowledge and technologies developed by the particle and nuclear 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 (Wilson, 1946) and the first patient was treated at the Lawrence Berkeley Laboratories, California (US), 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. 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. Nowadays, protons are used in 45 facilities, but also the use of Carbon ions is wider spread. The number of dedicated hadrontherapy centers is now rapidly increasing. As hadrontherapy is still relative an innovative therapy, there is a growing vivid debate about its cost-effectiveness (Lodge et al. 2007, Nakagawa et al. 2009, Lievens et al. 2013, Vanderstraeten et al 2014). On one hand, due to still scant evidence available in the past years, some medical expert claim against the promotion of a complex treatment modality compare to less-expensive modalities (Mills and Schulz 2015, Lodge et al. 2007, Olson et al. 2007). On the other, hadrontherapy centers are nowadays providing an increasing amount of clinical evidences, with a growing literature that finds it a very promising technology for several cancers treatment (Kamada et al. 2015; 2012, Lukens et al. 2015, Ishikawa et al. 2015, Shioyama et al. 2015, Combs et al. 2013a, 2013b, Ramaekers et al. 2013, Schlaff et al. 2014, Zips et al. 2013, Rieken et al. 2012, Koto et al. 2014).
Moreover, Hadrontherapy results more efficacious compare to traditional radiotherapy in reducing collateral effects of cancer therapy (Fagundes et al 2015, Torunn et al. 2016). .This promising development has been stated also by the ASTRO, American society for Radiation Oncology, (Allen et al. 2012) and the NCI has founded research program in this field (Marx V. 2014).
Finally, thanks to its radiobiological effectiveness hadrontherapy has proven to be the only walkable solution for a range of tumor types, i.e. those which are traditionally radio resistant to conventional treatment and cancers located very close to vital organs. Similarly, hadrontherapy is the only alternative available for those tumors for which radiotherapy was unsuccessful and surgery was not a feasible option. For these reasons it has to be not an alternative but a more scientifically advanced clinical solution as compared to radio therapy or other conventional treatments.

The CNAO

The CNAO is an infrastructure comprising two broad distinct areas but functionally integrated: the high technology components, made of a set of an accelerator and a set of 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 three treatment rooms, where the beam lines generated in the facility are used to deliver both proton and carbon ion therapy (Rossi, 2011). An experimental beam line with a dedicated room for research activities is currently under construction. Research development in the Hadrontheraphy field and the related decision to implement the CNAO is closely linked to the fundamental research in the field of Particle and Nuclear Physics. In fact the project idea stemmed from the intention to apply the knowledge about hadron accelerators developed at Italian Institute for Nuclear Physics (Istituto Nazionale di Fisica Nucleare – INFN) and CERN and further oriented for the delivery of cancer treatment by TERA foundation for Hadronterapy (Amaldi and Tosi, 1991). The idea was further developed and at CERN with the PIMMS (Proton Ion Medical Machine Study) project (Badano et al, 2000) and then finalized by means of a collaboration of researchers from CERN, INFN and medical research institutes. The construction of the centre began in the summer of 2005 and lasted until 2010.

According to Yin (2009), two main criteria guided the selection of CNAO as case study.
It is *representative* of applied research infrastructures in medical field. Specifically, CNAO enables the application of knowledge developed in the Particle and Nuclear Physics scientific field to innovative medical treatment. 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 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.
It is also a *critical* case study for testing all the dimensions of the Florio and Sirtori's CBA framework. Although hadronterapy is a very promising technology for cancer treatment, (see Fokas et al., 2009; Loeffler and Durante, 2013; MacDonald et al., 2012; Tsujii et al., 2014), it is more expensive than conventional therapy (it costs approximately EUR 20,000 per patient against EUR 6,000 of conventional therapy) as it exploits accelerators technology, sophisticated control and dose delivery systems, highly trained personnel as well as large hosting facilities (HIT, 2007). 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.

Data collection

According the need to cover different costs and benefit dimensions, multiple sources of evidence were combined using data triangulation (Yin, 2009):

- Documentary information. A systematic bibliographic review of CNAO project history was conducted that included articles in scientific journals, national and local newspapers and healthcare magazines. The search was performed using the Italian integrated library database, which provides access to the most significant private libraries and to all university and public national libraries. Moreover, reports from scientific and medical association has been consulted.
- Archival records. The research team have accessed to a number of official documentation and CNAO archives in order to retrieve data on medical treatment performed and administrative data on investment and operational cost, personnel organizational plan and human resources, visits to the RI by external visitor, suppliers. These documents and data were collected by mail and through on-site visits.
- A set of in-depth interviews with CNAO staff to understand the nature and technical specifications of the activities performed and types of services delivered and with the CNAO Health Director to evaluate patient demand and clinical protocols, instrumental to the calculation of benefits for patients;
- Semi-structured interviews with the representatives of six CNAO's supplier firms and the CEO of Detector S.r.l. (a company spin-off of CNAO), which have been identified as potentially benefitting of technological spillovers;
- Scientific publications and paper online repositories. A bibliometric research of articles produced by CNAO researchers was conducted in order to estimate the social benefit related to knowledge output. The search was performed using INSPIRE, PubMed and Web of Science search engines.

Table 1 Source of evidence breakdown by CBA dimensions

CBA dimension	Source of evidence
Past investment costs	Archival records - Administrative data
Past operating costs	Archival records - Administrative data
Future investment costs	Forecast – Administrative data
Future operating costs	Forecast – Administrative data
Knowledge output	Scientific publications and paper online repositories; CNAO internal archive
Technological spillovers	Semi-structured interviews
Human capital formation	Archival records and forecast – Administrative and Human Resources data
Cultural effects	Archival records – Communication office data Travel Planning Websites
Health benefits	Bibliographic review of articles in scientific journals; in-depth interviews with CNAO Health Director

Source: Authors

CBA basic assumptions

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).
- 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, considered the end year of the useful life of the CNAO synchrotron. 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.
- 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. 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 (IMF, 2013), has been applied to past values
- 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.
- In order to account for the uncertainty related to the necessary forecasting exercise, critical variables are treated as stochastic, i.e. expressed in terms of probability distributions functions rather than punctual 'best guess' values.

In the following sections baseline and ranges associated to the key quantities associated to costs and benefits of CNAO are identified, quantified and monetised. Baseline values refer to the most likely values used in the deterministic CBA model. Expected values instead refer to outcome values of the probabilistic analysis, implemented through a Monte Carlo simulation.

4 Results

4.1 Costs

The analysis of costs includes past and future investment costs and operating costs valued at shadow 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) 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 include: labour costs for the employes; 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. 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.
Besides investment and operating costs, replacement expenditures (e.g. short-life machinery and/or equipment such as beam sources and detectors) and future investment costs have to be considered, e.g. the new treatment room dedicated to research activities (its realization is planned to occur from summer 2014 to 2017). In addition, a constant activity of upgrading and optimisation of technological instruments is undertaken, in line with the at-the-edge nature of the activities carried out in the Centre.
The total discounted cost considered for the purpose of the CBA of the CNAO amounts to 465.9 million EUR over the 2002-2031 period. 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 based on experts' opinion.

Table 2 Investment and operating cost

	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

4.2 Applied research benefits on its users

4.2.1 Benefit for patients treated at CNAO

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 and this is the case also for hadrontheraty treatment (see Fokas et al., 2009; Loeffler and Durante, 2013; MacDonald et al., 2012; Tsujii et al., 2014) While these benefits are typical of all health infrastructures performing conventional treatments, specificities of CNAO is the inherent capacity to expand the scientific knowledge on the clinical benefits of hadrontherapy. In fact, hadrontherapy shows promising applications which are still at the infancy 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.

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. Drawing from the recent most relevant literature, formula (1) illustrates the authors' method to evaluate health benefits in the specific case of CNAO. In particular, this method refers to the human capital approach which has been adopted because of its relatively simple operationalisation and more conservative estimations. Further discussion on the existing literature is presented below (see section 'The economic value of life').

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

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 a Statistical Life Year
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.

Patients quantification

The yearly number of CNAO patients shown in Table 3 has been estimated assuming that during routine operation CNAO can treat around 1,000 patients per year and that the Centre will run at full capacity only from 2020 onwards. These estimates take into account the country demand forecast for protons and carbon ions therapy provided by the Italian Association of Radiation Oncology and the existing and future national supply of hadrontherapy treatments[1]. 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.

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

Table 3 Patient data breakdown by years

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 "yearly number of patients". Specifically, a lower and upper bounds of, respectively, 600 and 1,200 have been considered meaning that the variable "yearly number of patients" can assume all values between 600 and 1,200 with equal probability.

Marginal health improvements

At the time this analysis was performed, CNAO could treat clinical cases falling under 23 clinical protocols 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. Based on interviews with the CNAO Health Director, three types of benefits have been identified and linked to each treatment provided at CNAO (See Table 4).

Table 4 Types of benefits

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)	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.

Source: Authors based on in-depth interviews to CNAO Health Director.

Following the indications by the CNAO medical staff, each protocol has been associated with one of the mentioned types of benefits. 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, 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 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. Once the counterfactual treatments have been identified, the quantification of the marginal benefit arising from each protocol has been calculated as: i) marginal percentage of patients who fully recover compared to the counterfactual situation for benefit of TYPE 1 (Table 5); ii) marginal percentage of patients who gain some additional years of life thanks to hadrontherapy with respect to the counterfactual situation for benefit of TYPE 2 (Table 6); iii) marginal percentage of patients who benefit from a marginal increase in the quality of life compared to the counterfactual situation for benefit of TYPE 3 (Table 7). This third type of benefit can be incremental with respect to the other two types. Actually, a patient can gain the same life expectancy of the average healthy population (TYPE 1) or some additional years of life (TYPE 2) and for such number of years gained he/she can enjoy fewer side effects compared to the counterfactual scenario.

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. 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 on treatment toxicity 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 related to the effectiveness of treatments, a range of variation associated to the marginal percentage of patients who recover compared to the counterfactual arising from each protocol has been considered instead of punctual values. In particular, a standard deviation of 10% around the modal values presented in the Tables 5-7 has been used in the analysis.

All the marginal benefits have been thoroughly discussed with the CNAO medical staff. Lacking established evidence on the effectiveness of some of the treatments provided at CNAO due to their innovative nature the estimation of benefits 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.

Table 5 Marginal benefit of Type 1 by protocols

# of protocol	Pathology	Clinical alternative	Marginal percentage of patients who fully recover compared to the counterfactual situation
1	Proton radiation therapy for chordomas and chondrosarcomas of the skull base	No alternative	73%
2	Proton therapy of spine chordoma and chondrosarcoma	No alternative	73%
3	Proton therapy of intracranial meningioma	No alternative	33%
9	Carbon ion therapy of adenoid cystic carcinoma of salivary glands	Surgery + photon therapy	45%
10	Carbon ion re-irradiation of recurrent pleomorphic adenomas	Surgey	21%
11	Carbon ion re-irradiation of recurrent rectal cancer	No alterative*	45%
12	Carbon ion radiotherapy for bone and soft tissue sarcoma of cervico-cephalic area	No alterative*	14%
13	Carbon ion radiotherapy for bone and soft tissue sarcoma of trunk	No alterative*	33%
15	Carbon ion therapy of malignant melanoma of the mucous of the upper aerodigestive tract	Surgery + photon therapy	30%
16	Carbon ion therapy for high risk prostate cancer	Photon therapy	43%

19	Carbon ions therapy of primary malignant tumors of the liver	Photontherapy	36%

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.

Table 6 Marginal benefit of Type 2 by protocols

# of protocol	Pathology	Clinical alternative	Marginal percentage of patients who fully recover compared to the counterfactual	Number of life years gained with respect to the counterfactual
6	Proton boost for locally advanced cervico-cephalic area tumors	No alternative for advanced tumours	15%	5
8	Proton re-irradiation of recurrent spine chordoma and chondrosarcoma	No alterative	43%	3
14	Carbon ion therapy of recurrent cervico-cephalic area tumors	No alterative*	68%	0.5
18	Carbon ion therapy for pancreatic cancers	Palliative chemotherapy	40%	2
20	Carbon ion re-irradiation of recurrent spinal chordoma and chondrosarcoma	No alterative	43%	3
22	Protons and/or carbon ion integrated radiotherapy for poor prognosis in patients with operable sinonasaltumor	Surgey + photon therapy	10%	5
23	Protons and/or carbon ion integrated radiotherapy for poor prognosis in patients with inoperable sinonasaltumor	Photontherapy*	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.

Table 7 Marginal benefit of Type 3 by protocols

# of protocol	Pathology	Clinical alternative	Marginal percentage of patients who fully recover compared to the counterfactual	Number of life years gained with respect to the counterfactual	Quality of life adjustment factor*
7	Proton therapy of glioblastoma	No alterative	100%	1	0.3
21	Proton therapy of eye melanoma	Surgey	100%	15	0.3

Note: Protocols 4, 5 and 17 fall under this category. However, due to lack of evidence on marginal benefits compared to the counterfactual scenario, they have not been taken into account for precautionary reasons.

Source: Own elaboration based on interviews with CNAO medical staff.

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. Abelson, 2008 and 2010; Landefeld and Seskin, 1982; Sund, 2010; Viscusi and Aldy, 2003). 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:

$VOSL = \sum_{t=1}^{T-a} VOLY * (1 + r)$ (2)

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, Ashenfelter, 2006; OECD, 2010b, 2012; Sund, 2010; Viscusi and Aldy, 2003).

In this study, the human capital approach has been adopted because of its relatively simple operationalisation and more conservative estimations compared to either revealed or stated preference approaches. The human capital 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 (Landefeld and Seskin, 1982). The VOSL is calculated based on the lost production in terms of average annual wage due to a premature death of an individual. Specifically the following formula applies:

$$\mathrm{VOSL} = \Sigma_{i=1,T-t}(p_{t+1}\, Y_{t+1})/(1+r)^{i} \quad (3)$$

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.

Although accepted as a rule of thumb, this approach presents some shortcomings. It focuses only on the active working population and ignores the value of life of individuals which are excluded from the labor market. In order to mitigate such limit a slightly different approach to the standard human capital method has been applied. In particular, we have adapted the above formula of VOSL (3) considering per 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).

Based on the above adapted formula, a VOSL value for each of the six classes of age used for patient quantification has been calculated. This is the sum of discounted value of average per capita GDP each individual is expected to be endowed with until patient death (82 years). Then, the related VOLY value for each age class has been derived using formula (2). The average estimated values of VOLS and derived VOLY values are presented in Table 8.

Table 8 Value of VOSL and VOLY for the six 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 - social discount rate specifically calculated for Italy

Due to the level of criticality of VOSL values within the frame of our analysis, a benchmarking exercise with existing values retrieved from the literature and estimated following alternative approaches has been performed to set the boundaries of the triangular probability function assigned to the VOSL. 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.

Having established the range of variation of the three input variables (i.e. number of patients, marginal health improvement and economic value of a year of life saved), the total expected present value of the applied research benefit on CNAO's 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.

4.2.2 Benefit for users of experimental beam line

A high or medium energy experimental beam line is strongly demanded by researchers in 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). At present, the priority in the use of the beam line of the CNAO has been to clinical treatments; for research experimentsis it has been limited during the weekend and night. Therefore, the forthcoming beam line dedicated to experimental research will represent a steady service offered by CNAO to third users. An ad hoc survey carried out by CNAO before starting the construction of the beam line dedicated to research activities identified around 20 institutions manifesting their interest in using it. 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. 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. Considering a use of the beam of 8 hours a day for a number of days ranging from 200 to 225 per year after 2017, the expected present value of the benefit spilling-over from the use of the research beam is nearly EUR 45 million.

4.3 Value of knowledge outputs

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. In Florio and Sirtori, 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 cite the paper and valued through the opportunity cost of time employed by a scientists to read and understand someone else's paper and decide to cite it. They propose to use bibliometric techniques to measure RI's scientific output, quantifying the knowledge outputs generated by the "insiders" scientists (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. Particle therapy scientific community is relatively 'small' and rather young, therefore dedicated publications channels are still under development or relatively new, with limited coverage by reference database. For this reason, scientific output L0 has been retrieved through a combination of records extracted directly from the INSPIRE, PubMed, Web of Science websites and unpublished outputs such as conference proceedings made available by CNAO internal archive as well as founded in particle therapy thematic websites. To establish future projections of the first level papers (L0) it was adopted a non-linear model which assumes a peak in the number of papers in 6 years when the CNAO exits from the initial experimental phase, i.e. 2020. 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. According to a prudent approach, no other peaks are expected. 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, assuming that future papers L0 will be on average cited twice than those produced during the construction and the experimental phase.

According to Florio and Sirtori (2014), the average scientist's hourly compensation is considered a reasonable proxy of the marginal production cost of a paper. By analogy, the shadow price of citation is estimated using the opportunity cost of time employed by a scientist to read, understand someone else's paper and decide to cite it. Average gross wages were retrieved from Istat database and confronted with historical salaries paid by CNAO. Shadow wage has been assumed equal to market wage since the reference labour market is assumed to be open to international competition with easy mobility across countries. The share of time devoted to research is assumed to follow a triangular distribution with a modal value of 30%

for CNAO insider scientists and 80% for extra-CNAO scientists. 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 for CNAO insider scientists and of 5 papers for extra-CNAO scientists. These differences between CNAO insiders and extra-CNAO scientists are mainly due to the fact that CNAO staff is primarily devoted to clinical activities as compared to extra-CNAO staff. 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 a normal probability distribution with a standard deviation of 0.5 around the mean value of 30. Under these assumptions, 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. As for citations, assuming one hour as the average time needed to decide to cite a paper, the average hourly gross salary of scientists is taken as an estimate of the social value of one citation..

The expected present value of the knowledge output amount to nearly EUR 12.3 million, with ranges of possible values between EUR 6.3 and 27 million.

4.4 Technological spillovers

According to Florio and Sirtori (2014) model, technological spillovers involve the RI itself, e.g. through patents or spinoffs aiming at commercialize RI research breakthroughs, or technological externalities produced on the RI's supply chain. Moreover, they identified other RI's technological spill overs, derived as side effect of on-the-job working and learning by-doing process, remaining very often hidden and difficult to be estimated in monetary terms.

4.4.1 Technological externalities on the RI's supply chain

Florio and Sirtori (2014) propose to use the change of *net* output (i.e. incremental profit) directly imputable to the spill over effect, at shadow prices, to value technological externalities on the RI's supply chain. At this purpose, jointly with CNAO administrative office, the suppliers potentially beneficiaries of a sort of technological and knowledge transfer have been identified. Their products/service provisioning satisfies very specific technical requirements, duly customized to be fitting for the CNAO purpose. On the basis of data collected through semi-structured interviews to those selected suppliers, the average incremental profit can be approximated by a triangular probability distribution ranging from 1% to 10% with a modal value of 7%. The knowledge and technological skills derived by the collaboration with CNAO 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. 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.

The total volume of CNAO external procurement associated with the selected firms amounts to 25.2 million EUR (2013 constant prices). Adopting an average utility/sales ratio (increase turnover) with a uniform probability distribution ranging from 2 to 4, as derived by literature (Bianchi-Streit et al., 1984; Salina, 2006; Schmied, 1975), and considering the above mentioned average incremental profit margin, the suppliers' incremental benefit related to technological spill over is obtained. The discounted sum of benefit amounts to 6.5 million EUR in the baseline case.

4.4.2 Spin-off

An additional innovation outcome related to CNAO is the 2009 creation of a spinoff (De.Tec.Tor. S.r.l) aimed at commercialising the facility's research breakthroughs. 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. According to Florio and Sirtori (2014), 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. Since the activity of the spin-off will progressively detach from the technology endowment gained during the collaboration with CNAO, the time period for which the profits gained are considered in the CBA is 11 years. We considered yearly profits recorded from 2010 to 2014, profits estimated by the company for 2015 and a share of the profit estimated for 2015 for 2016 to 2020. The discounted sum of benefit amounts to nearly 1 million EUR in the baseline case.

4.4.3 Other technological spill overs

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 and CERN, which led to development of shared technological knowledge. Thanks to this collaboration, new expertise and knowledge have been developed involving not only technological development, but also a demanding clinical trial and experimental phase. This cumulative knowledge is a side-effect of on-the-job working and learning by-doing process not protected through intellectual property rights. This makes it difficult to attribute to CNAO a specific effect of such technological transfer observed in the scientific or industrial community. An experimental proxy to evaluate such category could be the transfer of this knowledge through specific contracts to similar centres, thus avoiding costs to undertake own tests and experimentations during the design and construction phase. A number of delegations from other centres have been visiting CNAO to collect information relevant for their activities. Among them, the MedAustron centre (Austria) purchased from CNAO the engineering design at a cost of approximately 8 million EUR. According to estimates made by CNAO managers, thanks to the purchased knowledge, MedAustron has benefitted a cost saving of approximately 14 million EUR due to avoided costs to develop design studies from scratch and to time savings to perform test and experimentations. This value can be considered a direct technological spill over 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 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.

4.5 Human capital formation

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, gained by RI's students and former employees, since the moment they leave the project. At CNAO, the human capital formation benefit is expected for students and young workers, such as: i) 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; ii) Researchers, remaining at CNAO up to 1 year, and who could be distinguished among fellows and doctoral students; iii) Interns, staying at CNAO for approximately 5 months for a stage, a training course or a specialization course; iv) Technical Medical Radiology Volunteers, remaining at CNAO for 3 months.

The number of persons belonging to the four mentioned categories arriving every year at CNAO has been retrieved from CNAO Personnel Statistics reports, available until 2013. For the period 2014-2031, the number of incoming university students/researchers/interns/volunteers has been stated with a normal distribution with standard deviation of 0.3 around the mean represented by 2013 value. The total number is 507.

The estimation of the benefit implies 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 to CNAO management and Human Resource office, the professional sectors where CNAO former students/young researchers are expected to find a job have been identified (i.e. other hadrontherapy facilities, research centres, academia, hospital, industry, and other sectors). Additionally, the share of students who find a job in one of the six mentioned sectors has been hypothesised.

The average salary for each of these professions, at four different career levels, has been retrieved from Istat databases. Using a logarithmic function, a continuous salary curve has been estimated for each professional sector and the average incremental salary by year of career has been calculated.

Concerning the incremental annual salary earned by former CNAO students/researchers, with a benefit transfer approach based on a LHC case study by Florio et al., (2015) it has been estimated 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%. Based on this range of variation and making the following two assumptions: i) CNAO students/researchers enter the labour market immediately after their experience at the CNAO; and ii) the incremental salary benefit is spread over their entire work career, lasting 40 years, the expected present value of the benefit for human capital formation is nearly EUR 15.4 million.

4.6 Outreach and cultural impact

Many research infrastructures organize outreach events and services aimed at informing the public on advances in science and technology. Florio and Sirtori (2014) suggest exploiting the CBA approaches to evaluate cultural tourism for scientific tourism as well estimating the willingness to pay of the general public for visiting the RI through the travel cost method. 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.

Since 2011, CNAO has organized free guided tours for students from high schools, universities, research institutes and scientific organizations, as well for general public. The number of visitors has been quantified taking into account the visitors for the period 2011-2014 and a maximum number of 1,800 visitors per year from 2014 onwards, considering capacity constraints.

Thanks to historical data of visits, five possible travel areas of origin and five different transport modes has been identified and an average travel cost (including lunches/accommodation, trip and the opportunity cost of time spent in travelling) has been estimated for each combination. The average cost and travel time has been retrieved from different travel websites. Almost 97% of visitors are supposed to remain for one day only, with a cost ranging from 8 to 12 EUR. The remaining nearly 3% of visitors are assumed to stay one night with a total cost ranging from 100 to 140 EUR per person. Based on the HEATCO travel time values related to working or leisure trips (HEATCO, 2002), the opportunity cost of time for different categories of visitors has been estimated. 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.

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.

4.7 The CNAO expected net present value

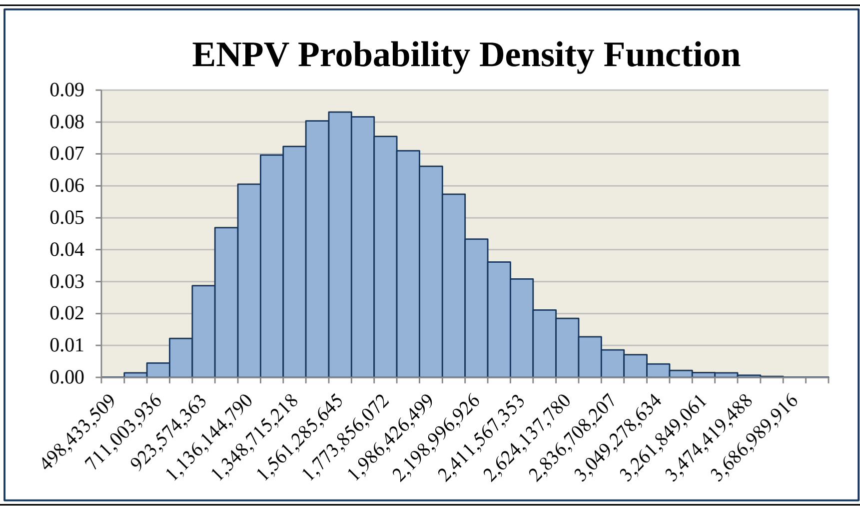
The results of the analysis, summarized in Table 9, show that over a time horizon of 30 years and under a number of rather conservative assumptions on forecasts, the RI is expected to provide net benefits amounting to approximately 1.6 billion discounted EUR (with a standard deviation of approximately 500 MEUR). In addition, risk analysis performed with the Monte Carlo simulation techniques (see results in Figure 1) 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.

Table 9 Baseline and expected values

Asset	Non discounted baseline value (Million Euro)	Discounted baseline value (Million Euro)	Share of total	Expected discounted value (Million Euro)	Standard deviation
TOTAL PAST INVESTMENT COSTS (2002-2013)	159.3	188.8	41%	-	-
TOTAL OPERATING COSTS (2002-2031)	315.8	248.5	53%	-	-
TOTAL FUTURE INVESTMENT COSTS (2014-2031)	28.6	23.8	5%	-	-
DECOMMISSIONING COST	8.0	4.7	1%	-	-
TOTAL COSTS	**511.7**	**465.9**	**100%**	**-**	**-**
HEALTH BENEFITS FOR PATIENTS	2,606.3	1,958.1	95.10%	2,028.6	495.7
BENEFIT FOR USERS OF THE EXPERIMENTAL BEAM	63.0	45.2	2.20%	45.1	3.7
KNOWLEDGE OUTPUT	14.9	11.7	0.57%	12.1	2.5
TECHNOLOGICAL EXTERNALITIES ON SUPPLY CHAIN	5.4	6.5	1.08%	22.6	2.0
SPIN-OFF	1.1	0.9			
OTHER TECHNOLOGICAL SPILLOVERS	14.5	14.9			
HUMAN CAPITAL FORMATION	35.6	15.4	0.75%	15.4	7.4
OUTREACH AND CULTURAL IMPACT	8.0	6.1	0.30%	6.2	0.9
TOTAL BENEFITS	**2,748.6**	**2,058.9**	**100%**	**2,130.0**	**-**

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

Figure 1 Economic Expected Net Present Value



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

Estimated probabilities

Pr. ENPV ≤ 0	0.000

Source: Authors

5 Conclusion

The paper aims at testing the pioneering Florio and Sirtori's CBA framework for the assessment of the net socio-economic impact of an applied research facility thus contributing to the scientific knowledge and theory in evaluating research infrastructure. In order to meet this goal an inductive case study was selected among applied research infrastructure in the healthcare sector.

The framework provides useful insights to measure benefits related to applied research infrastructure and to assess the relation between advancement in scientific knowledge and the materialisation of social benefits for users.

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.

Empirical testing shows that the composition of benefits of an applied RI is heavily affected by the category of benefits relating to the services provided by the infrastructure to its users. Particularly, the magnitude of the benefits produced to its patients is by far greater than any other benefit category. Indeed, CNAO is an health care *applied* RI and clinical treatments provided are the main application of knowledge and technologies developed by the nuclear and 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. It is therefore not surprising that most of the benefits are coming from the health improvements of patients due to the provision of hadrontherapy treatments, which qualifies as the direct application of research results to external users of the facility. The analysis confirmed 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. 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. Even under conservative estimation, benefits for patients from the hadrontherapy alone would overweight the total net present value of costs and therefore provide alone a proper justification for CNAO.

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, 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 Nuclear and 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. As mentioned above, the research carried out in the Centre is highly collaborative in nature, which led to development of shared knowledge and makes it difficult to attribute to the construction or operation of CNAO a specific effect of technological transfer observed in the scientific or industrial community. Moreover, 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. 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.

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