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ORIGINAL ARTICLE

Activity-based costing evaluation of [^{18}F]-fludeoxyglucose production

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Abstract
Introduction As healthcare expenses are escalating in many countries, the sector faces a new challenge of becoming more cost efficient. There is an urgent need for more accurate data on the costs of healthcare procedures. The cost of Positron Emission Tomography (PET) with [^{18}F]-fludeoxyglucose (^{18}F-FDG) studies is mainly influenced by the price of the radiopharmaceutical, which may vary throughout Europe from 300 to 500 Euro per patient dose (370 MBq). The aim of the current study is to conduct an activity-based costing (ABC) estimation of ^{18}F-FDG production in Europe to better identify the different cost components and to analyse their relative contribution to the total cost.
Materials and methods Financial data were collected on capital expense and global operating costs through interviews with industry experts, PET centre managers, evaluation of prior studies, and review of expenses incurred at the University Medical Centre in Groningen (The Netherlands). After mapping the activities, we divided the cost in five categories: wage, equipment, consumables, overhead and space costs. A sensitivity analysis was performed for key cost components, including the compliance with regulatory requirements.
Results The critical factor for profitability was throughput. Including the European regulation procedure, the cost for 370 MBq ^{18}F-FDG patient dose, 3 h EOS without delivery cost, ranges between 155 and 177 Euro/dose for two production runs and between 210 and 237 Euro/dose for one production run. These costs are predominantly determined by personnel and equipment costs, although the cost for quality assurance increases steadily.
Conclusion The ABC analysis provides significant insight into the production cost components of ^{18}F-FDG through different operating configurations. Reductions in equipment prices, increased availability of radiopharmaceuticals, growth in demand, and improvements in reimbursement will all contribute to the financial viability of this imaging technique.

Keywords Cost and cost-analysis · [^{18}F]-fludeoxyglucose · ^{18}F-FDG · Commercial production

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Introduction

Positron emission tomography (PET) with [^{18}F]-fludeoxyglucose (^{18}F-FDG) is a high-performance clinical imaging modality widely used in the diagnosis, staging, restaging and therapeutic monitoring of many common cancers [1–3]. Clinical PET plays also an increasing role in neurology and cardiology [4, 5].

Despite the well-documented clinical value of PET, operating a PET centre remains extremely complex and is widely perceived to be expensive. The cost of ^{18}F-FDG PET studies is mainly influenced by the price of the radiopharmaceutical, which may vary throughout Europe from 300 to 500 Euro per patient dose (370 MBq) [6].

Escalating health care expenses urge governments towards cost containment (e.g. limitation of the amount of centres, budget ceilings per medical speciality, the move towards prospective financing systems and increase in out-of-patients' pocket expenses). In this environment there is an urgent need for more accurate data on precise costs of health care interventions. Such cost information is useful for policy making (e.g. cost-effectiveness studies and reimbursement purposes) as well as for guiding internal management decisions [7–9].

In the beginning, ^{18}F-FDG was produced in an academic setting. This academically oriented PET production facility usually produces few patient doses per day for on-site use only. As the demand for ^{18}F-FDG has markedly grown, an increasing number of PET production facilities are now operated by for-profit corporate entities. Sometimes they contract with academic and medical institutions (many of which have a not-for-profit status) to manage the ^{18}F-FDG production at those institutions or they develop independent PET production facilities. The advances in radiochemistry and instrumentation for ^{18}F-FDG production have largely overcome the need of an on-site cyclotron and chemistry infrastructure, so that this radiopharmaceutical can be distributed commercially over relatively large distances.

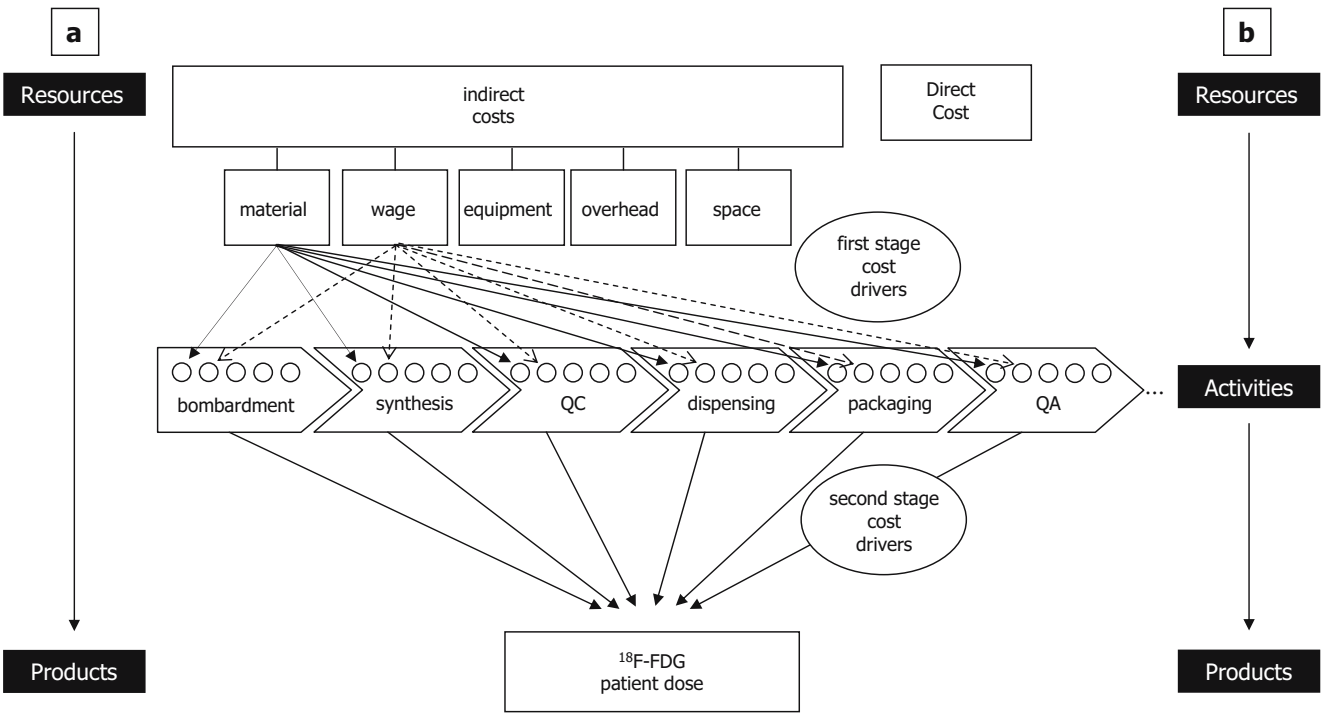
However, the economics of these two models of radiopharmaceutical production are similarly complicated by the properties of radioactive materials. There are considerable costs associated with engineering radiation protection equipment and procedures. Still more challenging and costly to address, though, are the difficulties related to radioisotopes' half-lives. The ^{18}F-FDG production is perceived to be complex and costly. This perception is in part due to the financial risk, including substantial up-front capital expenditures, the technical complexity leading to significant operational cost, and the added costs for satisfying regulatory requirements.

The purpose of this study is to conduct a comprehensive descriptive cost analysis based on an activity-based costing (ABC) method of the commercial ^{18}F-FDG production of a 370 MBq (10 mCi) ^{18}F-FDG patient dose to better identify the critical cost components, the distribution of costs across the different types of resources used, the added costs of satisfying regulatory requirements and the impact of changes in cost patterns. The cost calculation of the delivery fee is beyond the scope of our study.

Materials and methods

Design of the study

ABC defines costs in terms of an organization's processes or activities and determines their relative costs. The basic ABC assumption, represented in Scheme 1, is that cost objects consume activities, which in turn consume resources. With ABC, the process is subdivided into discrete, quantifiable activities or phases [10].



Scheme 1 Schematic representation of an activity-based approach. In contrast to conventional costing (*A*), where resources are allocated directly to products, ABC handles the production process as a series of activities (*B*)

For ABC, we used a four steps approach. First, department heads of academic and commercial production centres were interviewed to obtain key elements in the workflow that involves the ^{18}F-FDG production, followed by a second step involving in-depth, structured interviews of some key personnel of these centres.

Thirdly, information on resource unit costs was collected from the administration units from the PET centre of University Medical Centre Groningen (Groningen, The Netherlands) and reported during the different interviews to calculate an average cost.

It was an iterative process during 12 months to identify incompleteness and correct some errors or misinterpretations recorded during the interviews. Sensitivity analyses were undertaken on estimated variables in the study [11, 12].

Finally, based on these interviews, best and worst-case generic scenarios within realistic boundaries were build. The reliability of these different scenarios was confirmed by interviews of PET centre managers and most of the ^{18}F-FDG manufacturers. In that sense, the presented cost data are not the actual costs of one, or more, existing PET centre or a manufacturer, but they can be interpreted as the 'standard costs' of a ^{18}F-FDG production.

Methodological aspects

The ABC methodology is based on a stepwise process: (1) identification of the different activities in the production process, (2) the link between the different activities through cost drivers, (3) and how these activities are linked to the consumption of resources, which contains typically materials, wage, equipment, overhead and space costs.

Activity analysis

A commercial ^{18}F-FDG production process could be typically divided in five primary activities:

Production of fluoride-18 The commercial production of fluoride-18 is usually performed by a medium-sized cyclotron equipped with two to four targets. The number of production runs will be determined by the required activity. At the end of the irradiation, the fluorine-18 volumes are combined and delivered to the ^{18}F-FDG synthesis module located in the clean room.

^{18}F-FDG synthesis ^{18}F-FDG is manufactured in an automated chemical synthesis module from fluorine-18. In case of synthesis failure or multi-production, a second module is available. These modules are prepared within 15 min using disposable cassettes containing all required reagents. They ensure the recovery of the irradiated volume of enriched water as well as the purification of all toxic synthetic reagents and solvents. From fluorine-18, 50–60% yield ^{18}F-FDG could be obtained in about 35 min (without decay correction).

Quality control At the end of ^{18}F-FDG synthesis, 740 MBq (20 mCi) ^{18}F-FDG is sampled for quality control (QC) assessment according to the Europharmacopeia. About 30 min are spent for such tests; those for sterility and pyrogenicity are outsourced. According to GMP rules, production and the sterility control of ^{18}F-FDG have to be done in separate shielded and ventilated cleanrooms.

Dispensing and packaging phase An automated device frequently located in a hot cell of the cleanroom will dispense the PET drug into individual vials according to predefined calibrated activities. The ^{18}F-FDG vials are then transferred through a hatch to a dedicated area, where it is packaged in styrofoam and lead shielded packing for commercial distribution. The dispensing process lasts maximum 30 min depending on the number of vials to dispense. This time is also used to perform the QC before the batch release. The transport of these ^{18}F-FDG vials from commercial ^{18}F-FDG manufacturers to other PET operators in the immediate vicinity is also very time-sensitive. The total transport time, utilizing private air and ground couriers, to distant facilities could be evaluated around 120–180 min.

Starting from 300 GBq (8 Ci) fluoride-18 obtained by a dual target bombardment for 120 min, 150 GBq (4 Ci) ^{18}F-FDG could be produced. Taking into account the dispensing and shipping time, reasonably 32 to 34 patient ^{18}F-FDG doses of 370 MBq (10 mCi), calibrated at 3 h at the end of synthesis (3 h EOS), can be supplied, divided and shipped in a number of ways.

Secondary activities support the primary activities, but they are not linked to a specific product. Examples of such activities include general management, accounting and administration. The model allocates these secondary activities on the basis of the number ^{18}F-FDG production runs. The tertiary activities are the remainder space cost, mainly due to rooms without a specific activity (halls, stock rooms and kitchen), and remainder overhead costs (the land and property taxes and insurance) are also allocated at the end to the products by the number ^{18}F-FDG production runs.

Cost driver analysis

Once the structure of the different activities has been described through the activity analysis, the next step is the cost-driver analysis to describe their underlying relationship. A cost driver is the causal factor that influences the cost of an activity. In case of ^{18}F-FDG synthesis, the cost drivers, shown in Table 1 and determined using timeslots and questionnaires, are volume and time.

Table 1 Cost drivers per activity group used in model

Activities	Potential cost drivers	Cost driver used in the model
Production of fluoride-18	Number of doses, timeslots of PET studies	32–34 patient doses at 3 h EOS/run
Synthesis of ^{18}F-FDG	activity of fluoride-18, time of bombardment	dual target bombardment during 120 min, 300 GBq (8 Ci) fluoride-18
Dispensing	Number of doses, number of hospitals, time between the PET studies	32–34 patient doses at 3 h EOS/run
Packaging	Number of hospitals	32–34 patient doses at 3 h EOS /run
Quality Control	Number of batches,	Number of ^{18}F-FDG production batches
Waste management	Number of batches, number of doses	Number of ^{18}F-FDG production batches
Administration	Number of doses, number of hospitals	32–34 patient doses at 3 h EOS/run, not expressed in hospitals
General management	Number of personnel members, number of batches	6,5 FTE personnel for 1 or 2 production runs
Quality assurance	Number of modifications, number of procedures (sop's) and measurements	1 FTE personnel member, an "mean" amount for the modifications
Not allocated	Number of batches, number of penalties	Number of ^{18}F-FDG production batches, 0 to 10 production days failure

Some of the potential non-volume based cost drivers could be used, which could be a more refined reflection of the relation between the resource costs and activities and between the activities and products. The potential drawback of ABC systems lies in the time and management of such complex cost-accounting techniques. Because the precision of an ABC model depends critically on the level of detail of its constituting components, an appropriate choice of this level of detail is crucial. If the process analysis or the product definition is not detailed enough, the obtained cost per product will not be considered relevant because of a lack of specificity. Conversely, if too many (sub)activities and products are defined, the whole calculation process becomes too complex and difficult to perform

Cost estimation

In our model, five cost categories were defined: space, equipment, wage, materials and overhead costs. All the cost inputs were expressed in Euro, using 2006 activity and product data.

For the durable inputs, equivalent annual costs are calculated in Table 2 on the basis of the actual price or the current replacement value. An estimated clinical lifetime (n) of 5 or 10 years for medical equipment and 20 years for a cyclotron is usually accepted. Even if sometimes the lifetime of a cyclotron or hot cells may be longer, the technology will be severely altered at that time. Twenty years is also the estimated lifetime for the building taking into account its specific synthetic activities.

The space costs are allocated to the activities as a function of the activities taking place in the different rooms. The cost of some miscellaneous "common space" areas without specific function (corridors, kitchens) is allocated after the activity analysis through the number of production runs.

Between 350 and 400 m^2 is required for setting up a commercial ^{18}F-FDG production facility. The access to the vault is usually via a long, angled maze with multiple turns or through a blinded door. Globally, the additional space cost for the access is similar to the acquisition cost for the door. The experts estimate the European construction price ranging from 2,700 Euro/m^2 to 5,000 Euro/m^2 (Belgian rate: 4,500 Euro/m^2). This cost includes the basic equipment of the building (e.g. HVAC, electrical cabling, water, gas and product supply pipes to and from the cyclotron), which is similar to other high-technology facilities. Most of the space cost could be allocated in proportion to the activities. When different activities take place at the same space, a proportion of their cost was allocated in function of their time spent.

The equipment costs are composed by aggregation of the annual renting cost of the equipment, the wage costs of the technologist related to the equipment maintenance and the annual external maintenance. The equipment operating costs consist mainly of maintenance and repair. As a PET facility involves quite sophisticated equipment, most often, a maintenance contract with an external supplier is signed. The annual cost of such a contract often amounts to 8% of the equipment price.

To estimate the real wage cost, it is also necessary to wage cost variation during the day. We used what we think is a reasonable estimate and are fully aware of the fact that in practice, there are large variations. In the same time slot during the day, the personnel accumulates multiple activities. At the end of the day or during incomplete occupation, this accumulation of different tasks disappears. To take into account the variation of costs during the day, a slack time of 10% has been introduced.

With the increasing requirements to fulfil the regulatory standards, the personnel to run a ^{18}F-FDG production facility has grown dramatically. Radiopharmaceutical scientists, chemist technologists and cyclotron engineers are required. The two formers are responsible for ^{18}F-FDG production, quality assurance (QA), QC, dispensing, troubleshooting and

Table 2 Estimated annual cost of capital expenditures (Euros) relative to their estimated clinical lifetime

Capital Expenditure	Purchase Costs	Clinical lifetime (years)	Yearly equivalent Costs
Total construction costs		Total	130,932
Cyclotron/laboratory control interface area	630,000	20	50,553
Stockage area	45,000	20	3,611
Synthesis laboratorium	90,000	20	7,222
Dispensing	45,000	20	3,611
Packaging	45,000	20	3,611
Clean room	495,000	20	39,720
Waste area	22,500	20	1,805
Administration and accounting	64,800	20	5,200
General management	32,400	20	2,600
Quality assurance	64,800	20	5,200
Miscellaneous area (kitchen, corridor, etc.)	97,200	20	7,800
Total ^{18}F-FDG production costs		Total	208,798
Cyclotron acquisition /targets	1,400,000	20	112,340
Radiation safety monitoring	20,800	10	2,694
Hot-cells	255,000	10	33,024
FDG boxes	120,000	5	27,717
Dispensing equipment	155,000	10	20,073
Containers for transport	100,000	10	12,950
Total quality control and quality assurance costs		Total	36,846
QC equipment	175,000	10	22,663
Laboratory equipment	42,000	10	5,439
Radiation safety monitoring	28,620	10	3,706
IT equipment	3,750	5	866
Furniture	1,500	5	346
Central radiation protection systems software	16,560	5	3,825

Because of the opportunity cost of the durable inputs (lifetime >1 year), a correct calculation of the annual capital cost of with purchase price X, to be used for n years, is equal to $iX/[1-1/(1+i)n]$, assuming a real interest rate (i) of a 5%. The "purchase cost" represents the actual price or the current replacement value. The space costs (4,500 Euro/m^2) includes the engineering/architectural planning of the plant and an environmental impact study (all together 130,000 Euro)

adherence to GMP, whereas the latter takes care of cyclotron operation, maintenance and troubleshooting. Additional administrative support is needed to cope with the extensive paperwork for GMP documentation and accounting. The roles of these staff may overlap, and duties may vary depending on the degree of support provided by the cyclotron supplier. As resource requirements of personnel varied stepwise with the number of production runs, certain types of costs (semi-fixed costs) remain constant over a certain range (one and two runs). Five to six full-time equivalents (FTE) personnel are required for one to two batch productions: two to three FTE cyclotron operators, two FTE QC technicians, one and a half FTE administrative collaborators and two radiopharmaceutical scientists. In case of three productions, one FTE for the production and QC activities is added.

For the estimation of some wage costs, time-monitoring could be used (e.g. irradiation of the target). Other ones need interviews to check the time estimates (e.g. administration). To calculate the wage cost, we used reference wage cost based on an average seniority and on the mean cost per type of qualification for a University Hospital. The wage costs were allocated by multiplying the time spent for a specific activity by these reference wage cost.

The material costs are directly and unequivocally traced to the different activities. The non-specific space costs and the remainder overhead costs are allocated by the number of production runs.

The increasing use of ^{18}F-FDG in the clinical arena requires the reliable daily synthesis of large activities of ^{18}F-FDG. Although most facilities are fully operational over 95% of the time, commercial production sites sign back-up contracts with other productions sites to ensure reliable daily delivery and to avoid penalties. In a best case scenario, this back-up will be compensated with production failures of other distribution centres. In worst case, up to 10 annual failed productions will cost 99,000 Euro per production run (10 production days of 33 patient doses per batch at a list price of 300 Euro/patient dose).

Although the working hours in an average week and the holidays throughout the year differ throughout Europe, annual throughput capacity was determined by multiplying the number of runs per day by the annual number of production days. After excluding weekends and holidays (9 additional days per year), planned downtime (normally 12 to 24 days per year) and unplanned downtime (10 production days due to failed bombardments or syntheses per year), the resulting best and worst cases were 240 and 218 annual operating days.

A "best case–worst case" scenario within realistic boundaries was gradually built, and the sensitivity of the cost analysis was examined to determine how some key determinants affected to the ^{18}F-FDG production cost. In Table 3, the cost categories, cost types and cost units are summarized. When the process analysis was accomplished and the costs, activities and cost drivers were defined, the costs of the different activities were calculated (Microsoft Excel software).

Results

Baseline case

The global resource cost structure and the most important cost components are reported in Tables 3 and 4. In the

Table 3 Baseline annual costs per cost category and activity type

Resource items	Cost type	Annual cost	Unit cost
Primary activities			
Space (4,500 Euro/m^2)	Subtotal	130,633	m^2
Cyclotron shielded vault/laboratory control interface area	Fixed	57,553	140
Raw material stockage area	Fixed	4,111	10
FDG synthesis laboratory	Fixed	8,222	20
Waste area	Fixed	7,305	5
Dispensing area	Fixed	4,111	10
Packaging area	Fixed	4,111	10
Cleanroom	Fixed	45,220	110
Equipment (including service contract at 8%)	Subtotal	418,032	
Cylotron medium energy/2 targets	Fixed	224,340	
Four hot cells and 2 FDG boxes	Fixed	83,541	
One automatic dispensing unit	Fixed	52,546	
Quality control equipment	Fixed	36,663	
Laboratory equipment	Fixed	5,439	
Radiation protection equipment (including software)	Fixed	15,503	
Wage costs	Subtotal	310,000	FTE
Cyclotron operator	Semi-fixed	170,000	2
Quality Control technologist	Semi-fixed	70,000	1
QA responsible	Semi-fixed	70,000	1
Materials	Subtotal	140,150	
Enriched water (40 Euro/gram) and synthesis kit (110 Euro)	Variable	64,800	4 g ^{18}O
Utilities (power, gas)	Variable	27,350	
Quality control material (plates SIO2, KOH, gloves, etc.)	Variable	18,000	
Biological control	Variable	24,000	
Other	Variable	6,000	
Overhead	Subtotal	599,291	302,791
Decontamination fee	Fixed	96,291	96,291
Cleaning cost allocated through space costs (50 Euro/m^2)	Variable		
Regulation fees (multiple countries versus one country)		Multiple	one
Introduction regulation fee	Fixed	238,000	40,000
Initial compliance to GMP	Fixed	150,000	150,000
Maintenance of the regulation fee	Fixed	75,000	1,500
Annual Regulation fee modification (estimated)	Variable	40,000	15,000
Secondary activities			
Space (2,700 Euro/m^2)	Subtotal	15,999	m^2
Administrative rooms (administration, management, QA)	Fixed	15,999	60
Equipment (including service contract)	Subtotal	3,638	
Furniture	Fixed	1,039	
IT equipment	Fixed	2,598	
Wage	Subtotal	260,000	
Administrative	Semi-fixed	20,000	0.5
Accounting	Semi-fixed	50,000	1
Pharmaceutical scientist	Semi-fixed	190,000	2
Materials	Subtotal	14,400	
Other (paperwork, etc.)		14,400	
Tertiary activities			
	Subtotal	82,800	
Land and property taxes	Fixed	75,000	
Common space	Fixed	7,800	36 m^2
Back-up penalties (10 prod. days failure of 33 ^{18}F-FDG doses at 300 Euro)	Fixed	0	

These are the baseline costs for the production of 32–34 patient doses of 370 MBq ^{18}F-FDG (at 3 h EOS) based on 10% slack time, 240 production days (12 days planned downtime, no unplanned downtime), without back-up penalties and with regulation fees for one or multiple European countries. In the space costs we include also the cleaning activities, which are 50 Euro/m^2 .

Table 4 Baseline production cost of one ^{18}F-FDG batch per activity type

Activities	Equipment	Wage	Space	Material	Overhead	Total activity level
Production of fluoride-18	953	480	257	274	401	2,364.8 (37%)
Synthesis of FDG	321	80	34	110	-	545.4 (9%)
Dispensing	135	40	17	5	-	197.4 (3%)
Packaging	54	40	17	-	-	111.1 (2%)
Quality control	200	280	188	175	-	843.8 (13%)
Waste management	27	40	9	20	-	95.5 (2%)
Administration	5	280	27	20	-	331.7 (5%)
General management	5	760	13	20	-	798.4 (13%)
Quality assurance	31	280	27	20	369	726.2 (11%)
Not allocated	–	–	32	–	313	345.0 (5%)
Total at cost category level	1,731	2,280	622	644	1,083	6,359
Slacktime	173	228	62		108	
Total	1,904 (27%)	2,508 (36%)	684 (10%)	644 (9%)	1,191 (17%)	6,931

All the costs are expressed in Euro based on cost inputs of 2006. In a case of a regulation fee for one European country (marketing authorization fee, maintenance fee and modification fee) the overhead cost category in the QA will be 128 Euro instead of 369 Euro.

baseline case, the production-related activities consume 65% of all the production costs, with fluorine bombardment the utmost important cost component, whereas 35% is spent on support-related activities (mainly wage costs). The latter is often underestimated in academic environment when the personnel could be partially involved in research activities. The QC and QA have a growing impact consuming altogether 24% of the total production costs.

At cost category level (Table 3), the resource costs for one batch ^{18}F-FDG production is mainly determined by the wage (36%) and the equipment costs (27%), and to a lesser extend to overhead (17%), materials (9%) and space costs (10%).

Based on the baseline criteria (240 production days, a slack time of 10%, no back-up penalties and multi-centre regulation fees) and the number of daily batches, the production costs ranged between 5,129 Euro for two production runs per day and 7,823 Euro for one production run per day (Table 5). The operational costs of a commercial PET production facility are better characterized by the number of daily batches rather than by the number of doses.

Sensitivity analysis

Whereas no model can perfectly describe actual conditions, our economic assumptions are rather conservative. The cost for a 370 MBq patient dose, 3 h EOS without delivery cost, ranges between 155 and 177 Euro/dose for two production runs and between 210 and 237 Euro/dose for one production run (Table 5).

The ABC analysis allows a better understanding and management of PET facility cost structures by looking at variations in resources or practice patterns. To address areas of uncertainty of some assumptions and to determine the cost impact of key parameters, we varied the number of production days and the impact of the regulatory requirements in a one-way sensitivity analysis.

The number of production days One of the critical cost components is the number of production days. In case of planned downtime, back-up can be compensated by agreement with other regional radiopharmaceutical producers to ensure the coverage. Unplanned downtime will be only

Table 5 Sensitivity Analysis based on the number of production days and the number of back-up penalties

Production days	Number of runs			Cost/dose (33 doses)		
	1 run	2 runs	3 runs	1 run	2 runs	3 runs
European regulation procedure						
240 days (12 days planned downtime, no drop-off)	6,931	5,129	5,585	210	155	169
228 days (24 days planned downtime, no drop-off)	7,135	5,247	5,681	216	159	172
218 days (24 days planned downtime, 10 days drop-off)	7,823	5,854	6,269	237	177	190
National regulation procedure						
240 days (12 days planned downtime, no drop-off)	6,665	4,996	5,497	202	151	167
228 days (24 days planned downtime, no drop-off)	6,856	5,107	5,588	208	155	169
218 days (24 days planned downtime, 10 days drop-off)	7,531	5,708	6,171	228	173	187

compensated in the best case. In a worst case scenario, penalties for failure to supply must be introduced. In the worst case scenario using two production runs (Table 5), the 218 annual production days compared to 240 days increased the dose cost from 155 to 177 Euros, respectively. Increasing the slack time will have a similar cost impact as decreasing the annual production days.

Impact of the regulatory requirements Today, ^{18}F-FDG producers should comply with more and more rigorous regulatory standards similar to those required for unlabelled drugs. Complying with these standards requires additional upfront costs of personnel, office space and equipment. In addition, regulatory agencies have been increasingly moving toward a more stringent regulatory environment for manipulation and transport of radiopharmaceuticals.

This regulation has significant cost implications. An initial national marketing authorization costs 40,000 Euro and a European one 238,000 Euro. In addition, a 5-year maintenance fee needs to be paid ranging from 1,500 to 75,000 Euro for national or European authorization, respectively; a modification fee ranges from 15,000 to 40,000 Euro. Therefore, the annual amount spent depends on the type of certification and the number of modifications. In our model, QA costs represent 726 Euro per production (13% of the total cost) in a European regulation setting and 485 Euro per production (8% of the total cost) in a single-country setting. These costs mainly reflect the license fees and the additional wage cost. As regulatory compliance mainly affects the operating cost, they are typically independent of the size of the department.

Discussion

Traditional cost accounting methods are inaccurate, even sometimes misleading, and did not provide accurate cost information useful to internal management and policy making [7]. The major advantage of using ABC for cost calculation is that it yields more accurate costs. Costing is much more detailed and precise, and even more important, the percentage of unspecified allocated overhead costs diminishes drastically when ABC is used. Such information is also useful for internal management purposes and for healthcare policy making [7, 8, 13–18].

Although some assumptions could be debatable, the identification of various cost components of the ^{18}F-FDG production and the impact of their changes on the total cost will yield an accurate cost estimation model. The unit costs are reported in the paper to allow other centres to adjust calculations to their own settings and to facilitate comparisons across production facilities and countries.

There have still been only a few reports on implementations of ABC in health care [11, 12, 19–23]. The current ABC approach provides a better insight in the different cost components of ^{18}F-FDG production, including the added costs for complying with regulatory requirements. Such analysis becomes even more critical knowing that the cost of the radiopharmaceutical is the highest single expense of the cost of a ^{18}F-FDG PET study [6].

These annualized costs reflect the complexity of ^{18}F-FDG production, where the main costs are mainly determined by the wage (36%) and equipment costs (27%). Even with no other data available in the literature on production costs, the operational time has similar influence as in other "very expensive" medico-technical procedures (e.g. the operational costs in radiology and radiotherapy departments). ABC can be integrated with Total Quality Management, employee empowerment, and many other changes taking place in modern health care management today. This approach helps identifying opportunities to improve process effectiveness and efficiency.

Instead of other ABC approaches, we observe a relatively high amount of overhead costs (17%) due to the regulation fees and other regulatory requirements (e.g. decontamination fee). Moreover, this costing exercise shows policy makers also how the total cost is more and more affected by the QA-related activities [11, 12, 20, 22]. The QC and QA (without the regulation fees) have a growing impact consuming altogether 24% of the total production costs. It is important to notice that in the calculation of the costs due to QA, we were not able to separate the cost component of constructing a facility compliant with radiation safety and GMP requirements [19].

These results need to be examined in the light of study limitations. First, the amount of overhead costs could probably be further reduced, but at the cost of having to collect and process larger quantities of information. The precision of an ABC system depends critically on the level of detail of its constituting components. A high level of detail, however, unavoidably translates into a higher workload (and cost), not only during the development phase, but also in daily use. Different choices need to be made about the desired complexity to maintain the model practically manageable [11, 12, 22].

Furthermore, the building site was not included. Although in a hybrid academic/commercial situation, the university often grants the land, the cost for a 2,000 m^2 plot of land (at 750 Euro/m^2 amortized over 20 years) will account for less than 5% of a base case production cost.

Another limitation of the study is its economic approach different from a pure accounting approach in a various number of ways: (1) buildings and equipment value at their replacement cost rather than their historical purchase price, (2) the opportunity cost of capital for all durable assets by

calculating the annual equivalent cost, and (3) the initial investment cost of durable assets is spread over their expected clinical lifetime of each piece of equipment, this clinical lifetime need not coincide with the lifetime assumed in the accounting data [24].

Finally, the patient dose is usually based on 370 MBq 3 h end of synthesis. These numbers were based on the administered dose required on BGO PET camera taking into account an average 2 h delivery time. With the development of faster PET-CT system, the acquisition time may be as three times lower or the administered dose reduces at the same extent. Moreover, the delivery time may be quite variable depending on the PET density in the area. Finally, the ^{18}F-FDG demand may vary day to day; therefore, the required number of doses may affect the production planning from one to several runs a day. Since the production, distribution and likely volumes of studies from an individual producer are limited by the intrinsic properties of ^{18}F-FDG, the economic model must accommodate these possibilities as well. Keeping in mind these particular features, the exact number of cyclotrons required in Europe and the "precise" cost per production are hard to predict.

From a well-equilibrated balance among the ^{18}F-FDG production costs, adequate payment rates, and the expanded reimbursement coverage will depend the European growth in the number of clinical PET operations. Better understanding and standardization of cost analyses are especially important when promoting expensive imaging modalities, such as PET-CT even with new radiopharmaceuticals, in a medical world more and more driven by economical considerations.

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