# Budget impact of implementing platelet pathogen reduction into the Italian blood transfusion system

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**Background.** Despite improvements in blood donor selection and screening procedures, transfusion recipients can still develop complications related to infections by known and emerging pathogens. Pathogen reduction technologies (PRT) have been developed to reduce such risks. The present study, developed whithin a wider health technology assessment (HTA) process, was undertaken to estimate the costs of the continuing increase in the use of platelet PRT in Italy.

**Materials and methods.** A multidisciplinary team was established to perform the HTA and conduct a budget impact analysis. Quantitative data on platelet use were derived from the 2015 national blood transfusion report and from the Italian Platelets Transfusion Assessment Study (IPTAS). The current national fee of 60 Euro per platelet PRT procedure was used to quantify the costs to the Italian National Health Service (INHS). The analysis adopts a 3-year time-frame. In order to identify the impact on budget we compared a scenario representing an increased use of PRT platelets over time with a control scenario in which standard platelets are used.

**Results.** Progressive implementation of PRT for 20%, 40% and 66% of annual adult platelet doses could generate an increase in annual costs for the INHS amounting to approximately 7, 14 and 23 million Euros, respectively. Use of kits and devices suitable for the treatment of multiple adult platelet doses in one PRT procedure could lower costs.

**Discussion.** In order to fully evaluate the societal perspective of implementing platelet PRT, the increase in costs must be balanced against the expected benefits (prevention of transfusion-transmissible infections, white cell inactivation, extension of platelet storage, discontinuation of pathogen detection testing). Further studies based on actual numbers of platelet transfusion complications and their societal cost at a local level are needed to see the full cost to benefit ratio of platelet PRT implementation in Italy, and to promote equal treatment for all citizens.

**Keywords:** platelet transfusion, pathogen reduction technology, transfusion risks.



## Introduction

The implementation of progressively improved measures aimed at reducing the risk of transmission of viral infection has significantly increased the safety of blood transfusion[1-4]. The current risk is very low for a number of known viruses, such as HCV, HBV and HIV, which can be detected accurately in the donor blood by using well standardised and highly sensitive laboratory assays[5,6]. However, the risk cannot be determined *a priori* or promptly avoided when novel infectious agents enter the blood supply[7,8]; recent examples of the latter are the Zika and Chikungunya epidemics which have affected large numbers of individuals in different countries[9,10], including Italy[11,12]. The measures adopted to reduce risk include deferral of donors travelling to endemic areas, which is the only effective procedure until specific donor screening assays are developed, validated and distributed by industry. Becuase of their very nature, these measures (deferral of donors and donor screening tests) have been categorised as 'reactive'[13,14]. In spite of their recognised efficacy, implementation of reactive measures takes time, significantly reduces the available donor pool, and requires significant economic and organisational resources.

To overcome these limitations, a preventive approach has been developed which uses procedures collectively termed 'pathogen reduction technologies' (PRTs)[15-17]. PRTs are based on photochemical treatments with controlled UV light illumination, which covalently modify the nucleic acids present in viruses, bacteria, parasites and white cells, thus preventing their replication and transcription. Therefore, PRTs can decrease not only the risk of transmission of viral infections, but also of septic reactions caused by bacterial contamination of blood components. This complication is of particular concern in platelet transfusion recipients, as platelet components are more vulnerable to bacterial contamination than other blood components owing to their higher storage temperature (20-24 °C). Moreover, PRTs offer protection against immunological complications caused by viable HLA incompatible white cells present in allogeneic blood components and consequently gamma irradiation is not needed for their prevention.

Specific PRTs which offer good transparency to UV light illumination have been developed and approved for commercial distribution of platelets and plasma. PRTs for whole blood and red blood cells are in an advanced experimental phase[18,19].

The Italian Ministry of Health was interested in determining the cost to benefit ratio of mandatory implementation of platelet PRT in Italy. To this aim, a clinical trial named the Italian Platelets Technology Assessment Study (IPTAS; *clinicaltrials.gov identifier: 01642563*) was carried out to evaluate consumption and clinical efficacy of platelets treated with two commercial PRTs as compared to conventional non-PRT platelets[20-22]. Furthermore, a health technology assessment (HTA) of platelet PRT based on national data on platelet use and on IPTAS data was carried out by a multidisciplinary team.

This article presents a budget impact analysis (BIA) developed within the economic domain of the HTA. The aim of this analysis is to estimate the incremental cost of implementing Intercept® (Cerus, Concord, CA, USA) and Mirasol® (Terumo BCT, Lakewood, CO, USA) platelet PRT in Italy.

## Materials and methods

### Health technology assessment

A multidisciplinary team of experts, including clinicians, a biomedical engineer, health economists, experts in HTA methodology, and bioethicists, was established. Subgroups of the working team were identified and assigned one or more HTA domains described on the EUnetHTA Core Model[23-29].

### Budget impact analysis

Within the economic domain of the HTA, a 3-year horizon BIA comparing two scenarios was performed. The first scenario foresees a progressively increasing proportion of PRT platelets treated with the Intercept® and Mirasol® technologies, from 10% each in the first year up to 33% each in the third year; these proportions were arbitrarily chosen to provide estimates of a progressively increasing application of platelet PRT in Italy. The second scenario involves the use of standard platelets only.

The target population of this analysis is made up of patients transfused with platelets in Italy (51,885 individual patients in 2015)[30]. We used the current national tariffs for non-PRT platelet components for gamma irradiation and PRT procedures (Table I)[31] and data on platelet production from the 2015 annual report of the Italian blood transfusion system (Table II)[30]. Our analysis included the different types of platelet products used in Italy in 2015: platelet pools prepared from buffy-coat or the platelet-rich plasma methods, monocomponent and multicomponent platelet apheresis. The types of platelet components considered for our study are referred to the year 2015, but it is important to note that, since 2016, production of platelet-rich plasma concentrates is no longer allowed in Italy[32]. However, this change does not affect the study results.

**Table I -** National cost for adult platelet doses prepared with different methods, for gamma irradiation and for pathogen reduction technology procedures (euros/adult platelet dose).

| Item | Value (€) |
|---|---|
| Adult platelet dose >$3\times10^{11}$ prepared by mono-component apheresis | 418 |
| Adult platelet dose >$2\times10^{11}$ prepared by multi-component apheresis | 256 |
| Adult platelet dose >$2\times10^{11}$ prepared by buffy coat or platelet-rich plasma method | 97 |
| Gamma irradiation procedure/adult platelet dose | 19 |
| PRT procedure | 60 |

PRT: pathogen reduction technology.

**Table II -** Number (n.) and cost (in euros) of non-pathogen reduction technologies (PRT) adult platelet doses prepared in Italy in 2015 with different methods.

| Item | Value[30] | Annual cost (€) |
|---|---|---|
| N. of adult platelet doses >$3\times10^{11}$ prepared by mono-component apheresis | 12,668 (4.6%) | 5,295,224 |
| N. of adult platelet doses >$2\times10^{11}$ prepared by multi-component apheresis | 66,506 (24.1%) | 17,025,536 |
| N. of adult platelet doses >$2\times10^{11}$ prepared by buffy coat or platelet rich plasma method (pool of 5) | 197,235 (71.3%) | 19,131,795 |
| Total n. of prepared adult platelet doses | 276,409 (100%) | 41,452,555 |

The average number of units transfused per patient was estimated on the basis of the IPTAS study, a prospective randomised clinical trial which evaluated the efficacy of platelet transfusion in 212 onco-hematologic patients receiving chemotherapy or allogeneic hemopoietic transplant transfused with PRT platelets, as compared to 212 control patients transfused with standard platelets. Detailed results of the IPTAS study have been published elsewhere[20,21].

The study showed similar frequencies of bleeding events and higher blood component use in recipients of PRT *versus* standard platelets. With relevance to the present HTA, IPTAS showed that mean platelet use in PRT-treated patients *vs* controls was 54% higher [95% confidence interval (CI): 36%-74%] and 34% higher (95% CI: 16%-54%) for Intercept® and Mirasol® platelet recipients, respectively.

Platelet PRTs use illumination devices which deliver controlled doses of UV light to platelets. The main differences between the different commercial PRTs involve the spectrum of UV light used for illumination, time and dose of illumination, use of added photo-active substance, and the requirement for compound adsorption at the end of the procedure. Details on the different PRTs are available in the manufacturers' instructions for use. Specific features of platelets PTRs are reported in the literature[33-36].

## Results

Results of the BIA are reported in Table III and are calculated on an assumed incremental requirement of Intercept® and Mirasol® PRT platelets of +54% and +34% *vs* standard non-PRT platelets, respectively.

A net annual cost increase (NAIC) of 41 Euro per PRT adult platelet dose was set against the incremental cost of 60 Euro per PRT procedure (national cost) and the decremental cost of 19 Euro made from discontinuation of gamma irradiation for PRT platelets (Table III). Euro values are rounded off to the nearest euro. It is seen that treating 66% of platelets with PRT would increase the annual cost of platelet procurement in Italy from 41,452,555 to 64,261,037 Euros, with a differential annual cost of 22,808,482 Euros.

## Discussion

A number of studies reported in the literature[20,21,37-42] and their meta-analyses[43-46] support the clinical safety of platelets treated with commercial PRT procedures. Their implementation into routine practice of blood centres and establishments was easily managed in many institutions by specific training of staff in charge of blood component preparation and training clinicians on their use[47-52].

Based on the above evidence, which supported the mandatory adoption of PRT in some countries, and on the public desire to receive "zero risk" treatments, it can be expected that the clinical demand for PRT-treated blood components will grow in the near future. However, the positive findings and perspectives reported here should not lead the transfusion medicine community and the health administrators in charge of resource allocation to ignore the following issues: i) pathogen reduction of plasma and platelets with current commercial procedures is not equally effective on all the pathogens tested; ii) PRTs are not available for all blood components, as PRTs for whole blood and red blood cells are still in the experimental phase; and iii) some detrimental alterations have been documented in

**Table III -** Results of budget impact analysis.

| **Scenario 1** | | **Year 1** | **Year 2** | **Year 3** |
|---|---|---|---|---|
| Standard platelets | Share | 0.80 | 0.60 | 0.34 |
| | Cost of adult doses | € 33,162,044 | € 24,871,533 | € 14,093,869 |
| Intercept® platelets | Share | 0.10 | 0.20 | 0.33 |
| | Cost of adult doses | € 6,383,693 | € 12,767,386 | € 21,066,187 |
| | NAIC | € 1,745,246 | € 3,490,492 | € 5,759,312 |
| Mirasol® platelets | Share | 0.10 | 0.20 | 0.33 |
| | Cost of adult doses | € 5,554,642 | € 11,109,284 | € 18,330,319 |
| | NAIC | € 1,518,591 | € 3,037,182 | € 5,011,350 |
| ***Total*** | Total cost | € 48,364,216 | € 55,275,877 | € 64,261,037 |
| **Scenario 2** | | **Year 1** | **Year 2** | **Year 3** |
| Standard platelets | Share | 1.00 | 1.00 | 1.00 |
| | Cost of adult doses | € 41,452,555 | € 41,452,555 | € 41,452,555 |
| **Scenarios 1 - 2** | Balance | € 6,911,661 | € 13,823,322 | € 22,808,482 |

Scenario 1: progressively increasing proportion of pathogen reduction technology platelets treated with the Intercept® and Mirasol® technologies, from 10% each in the first year up to 33% each in the third year; Scenario 2: use of standard platelets only.
NAIC: net annual increased cost.

PRT treated blood components. In this regard, a number of clinical trials have shown decreased post-transfusion platelet count increments in recipients of PRT platelets. Moreover, recent studies do not exclude the possibility that some PRTs can induce mitochondrial damage, the clinical relevance of which in platelet recipients needs to be determined[17,35].

The present study was undertaken to estimate the costs of a progressively increased adoption of platelet PRTs in Italy, in view of their possible mandatory adoption in the future for all platelet components.

Our analysis showed that implementing PRTs for two-thirds of platelets transfused in Italy would generate an annual incremental cost of approximately 23 million Euros. Obviously, costs would be greater with the implementation of PRT for all platelet units. Our estimates apply to PRT procedures carried out individually for each adult platelet dose. It should be noted that savings could be made with the use of recently developed procedures allowing the simultaneous PRT treatment of multiple adult platelet doses with one disposable kit.

Our study has important limitations as it would be important to report the full cost to benefit ratio of PRT implementation in Italy. This was not possible since complete information on the number of patients developing transfusion-transmitted bacterial infections and their societal costs was not available. Data collected in the haemovigilance section of the National Blood Information System (SISTRA) (*unpublished data*), for the period 2010-2015, report 5 cases (mean value was 0.83 cases per year) of transfusion-transmitted bacterial infections (TTBI) with 1,289,063 adult therapeutic doses (ATD) transfused (one TTBI every 257,813 transfused ATD). In this regard, it is well-known that even mature haemovigilance systems suffer from an under-reporting of these adverse events and that complete reporting takes a long time and requires significant organisational efforts[53,54]. Moreover, uncertainty on the economic impact of a possible extension of platelet storage from 5 to 7 days prevented us from factoring this element into our model. In spite of these limitations, the study can provide useful information to health managers in charge of allocating resources from finite budgets to competing medical interventions.

**Table IV -** Selected outcomes of cost analyses on pathogen reduction technology (PRT) implementation in different countries.

| 1st author, year, country | Results |
|---|---|
| Bell, 2003, USA[55] | Incremental cost per quality adjusted life year (QALY) gained by using PRT *vs* standard apheresis platelet ranged from US $ 1,308,833 to 4,451,650 (without bacterial testing) and US $ 4,759,402 to 22,968,066 (with bacterial testing). Corresponding figures for PRT pooled platelets ranged from US $ 457,586 to 1,816,060. |
| Staginnus, 2004, Japan[56] | The authors reported that "the cost-effectiveness of the IBS for platelets is comparable with and potentially better than that of other blood safety interventions (e.g., nucleic acid testing) and, in general, other recently implemented safety interventions (e.g., chemical regulations and traffic safety measures) accepted as valuable in Japan". |
| Janssen, 2006, the Netherlands[58] | The cost per QALY gained with PRT platelets was US $ 496,674. |
| Moeremans, 2006, Belgium[59] | Incremental cost-effectiveness ratio "ranged from 3,459,201 euro/QALY in absence of emerging pathogen to 195,364 euro/QALY". |
| Custer, 2010, Canada[60] | Whole blood PRT was estimated to have a cost-effectiveness of $ 1,276,000/QALY compared to current screens and interventions. Platelets and plasma PRT was estimated to have a cost-effectiveness of $ 1,423,000/QALY on an all transfusions bases. |
| Agapova, 2014, Poland[64] | Implementation of plasma PRT was estimated to cost 610,000 euros per QALY; implementation of both plasma and platelets PRT had a lower cost of 348,000 euro per QALY. |
| McCullough, 2015, USA[63] | Costs of tests that could be eliminated with the implementation of PRT totalled US $ 71.76/unit. Additional savings of US $ 2.70/unit could be expected due to a decrease in transfusion reactions. |

## Conclusions

Our findings should be considered together with those of other authors who have determined the cost-effectiveness of PRT implementation in other countries[55-64], with possible cost incremental variations over time[65], and with public acceptability of PRTs[66]. Table IV reports selected outcomes of published studies, which may facilitate the discussion and development of operative decisions in our country before local data on the expected benefits of PRT implementation can be gathered and valued. Besides economical considerations, regular monitoring of patient safety is and will be of paramount importance, also in view of very recent findings suggesting that platelet concentrates treated with a riboflavin-based PRT may show increased risk of platelet-specific alloimmune responses due to enhancement of storage-induced apoptosis[67].

Finally, the HTA of platelet PRTs should be periodically up-dated in view of the progress on PRTs for whole blood and red blood cells[19,68-75] to promote equal treatment for all citizens.

## Authorship contributions

The current report is the result of a joint effort between the Graduate School of Health Economics and Management (Altems) - *Università Cattolica del Sacro Cuore* (UCSC) and the Italian National Blood Centre (INBC). This research project, led by Prof. Americo Cicchetti, Director of Altems, involved

Prof. Giancarlo M. Liumbruno, Director of the INBC, seven clinical experts from the INBC, a biomedical engineer from Altems, four health economists from Altems, a health economist and a clinical expert from the Health Technology Assessment Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, and four bioethicists from the Institute of Bioethics and Medical Humanities, Fondazione Policlinico "A Gemelli" IRCCS, Università Cattolica del Sacro Cuore (two with a clinical background, one with legal background and one with a background in philosophy).

This manuscript reports a budget impact analysis developed within a wider HTA process performed by a multidisciplinary group. In detail, Rebulla P., Marano G., Farina B., Pati I. Veropalumbo E., Pupella S., Liumbruno G.M., experts from the INBC, focused on the clinical aspects related to the technologies under study such as current use, description and efficacy; Fiore A., from Altems focused on the safety profile of the technologies; Coretti S., Rumi F., Sacco F. and Cicchetti A. from Altems focused on the cost-analysis; Di Bidino R. and Urbina L.I. from the HTA unit of Fondazione Policlinico Gemelli dealt with organizational aspects; finally, Refolo P., Sacchini D., Spagnolo A.G., and Midolo E. from Institute of Bioethics and Medical Humanities of Fondazione Policlinico Gemelli focused on ethical, legal and social issues concerning the use of these technologies. The overall internal review of the document, prior to dissemination, was performed by Prof. Rebulla P., Prof. Liumbruno G.M. and Prof. Cicchetti A.

### Disclosure of conflicts of interest

*GML is the Editor-in-Chief of Blood Transfusion and therefore this manuscript has undergone additional external review. The other Authors declare no conflicts of interest.*

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