## Introduction

Applying optimization methods to healthcare management and logistics is a developing research area with numerous studies. Specifically, facility location, staff rostering, patient allocation, and medical supply transportation are the main themes analysed. Optimization approaches have been developed for several healthcare related problems, ranging from the resource management in hospitals to the delivery of care services in a territory. However, optimization approaches can also improve other services in the health system that have been only marginally addressed, yet. One of them is the Plasma Donation (PD) system, aiming at providing an adequate supply of plasma to Transfusion Centres (TCs) and hospitals.

Plasma is necessary for several treatments and surgeries, and still a limited resource. The need for plasma is about ten million units per year in the USA, 2.1 in Italy and 2 in Turkey; moreover, people still die in some countries because of inadequate supply of plasma products (World Health Organization 2014). Hence, PD plays a fundamental role in healthcare systems, aiming at guaranteeing an adequate plasma availability to meet the demand and save lives. In Western countries, plasma is usually collected from *donors*, i.e., unpaid individuals who give plasma voluntarily. Plasma is classified into groups (A and subgroups, B, 0 or AB) and based on the Rhesus factor (Rh+ or Rh-), and each donor should be correctly matched with the patient who receives his/her plasma. Moreover, as it may transmit diseases, plasma must be screened before utilization.

Generally, there are two types of donation: whole-plasma donation, in which the whole plasma is directly collected in a plastic bag, and *apheresis*, i.e., the donation of specific components in which a mechanical gathering unit decays the required plasma parts.

Plasma requires particular precautions for collection and storage, and its shelf life from donation to utilization is limited, thus requiring a continuous feeding of the system (Greening et al. 2010). Hence, a successful PD supply chain should meet the daily demand of plasma and follow its temporal pattern. According to Sundaram and Santhanam (2011), PD supply chain and the related management problems can be classified based on the main phases of a plasma bag life: donor registration, plasma collection, plasma screening/evaluation, inventory storage and delivery. A slightly different classification is proposed in Pierskalla (2004), according to which the management of PD supply chain concerns both strategic decisions (e.g., location of plasma centres) and tactical operational decisions (e.g., production of multiple products, control of inventory levels, plasma allocation to hospitals, and delivery to multiple sites). In our review, we refer to the first classification scheme.

Many papers address the management of the PD supply chain (see Belien and Forcé (2012) for a recent survey); however, there are still some open issues. The aim of this paper is reviewing the literature related to the PD system management and classifying the existing research based on the process phase, in order to highlight unexplored issues and to point out alternative perspectives and possible future research opportunities. In section "Phases of Plasma Donation System" we give details about the PD system and survey the existing literature (review updated at December 2014); then in section "Discussion and Open Issues" we discuss the open issues and propose future research directions.

## Phases of Plasma Donation System

PD supply chain can be divided into four main steps, as reported in Fig. 1: collection, transportation, storage and utilization. First, the plasma is collected: donors are checked in plasma centres to assess their eligibility and, if eligible, they make the donation. Once the plasma is gathered, tests are independently performed on each individual's plasma in order to prevent infectious diseases (screening process). Afterwards, the plasma is transported and stored. Components are then distributed to the hospitals based on their inventory needs. Finally, it is transferred to the final users for transfusion.

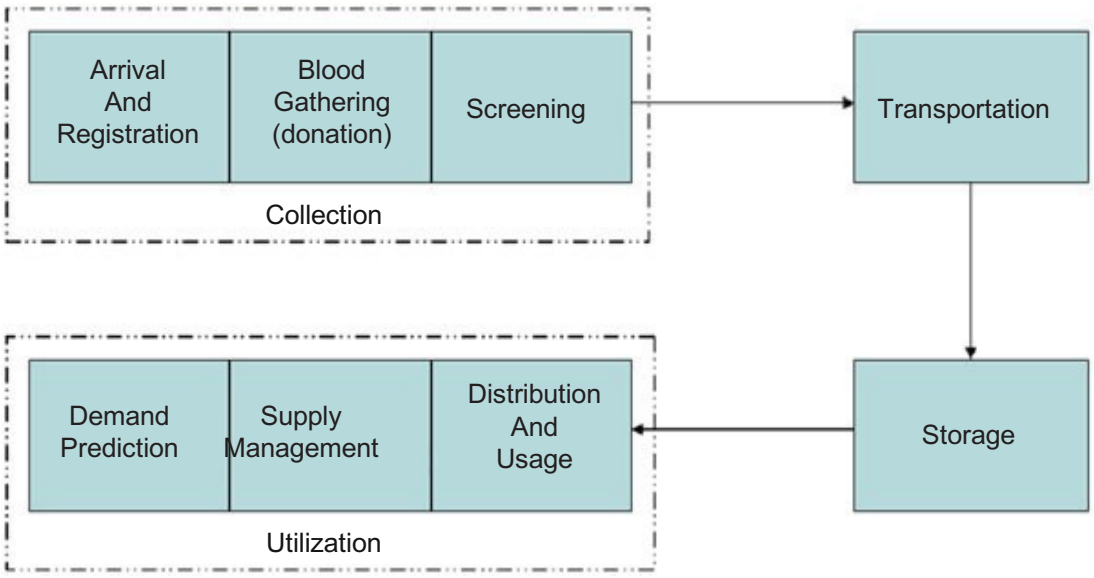


**Fig. 1** Phases of the life cycle of a blood bag

## Donors, Plasma Collection and Screening

PD process starts with the arrival of the donor at the plasma center. Donors can be divided in returning donors, who donate on an almost regular basis, and walk-in donors, who are entering the system occasionally or for the first time. In any case, donations can be made after a defined rest period from the previous one, which is defined by law. As donors have a crucial importance in the system, their availability, frequency and motivation have been studied from both a statistical and a social perspective.

### Social Aspects

The main reasons for plasma donation and their relative importance have been studied by Bani and Giussani (2011). Moreover, it is also documented that the organization of plasma collection phase may have an impact on donors' availability. Poor treatment, poor staff skills, and a bad experience are the main reasons of not returning to donate (Schereiber et al. 2003). Also prolonged queuing times are negatively correlated to PD satisfaction (McKeever et al. 2006; Katz et al. 2007). Hence, a well-organized donation management has a strong impact on the availability of plasma bags, and also on donors' motivation, thus possibly increasing/decreasing their availability.

### Donor Arrival and Registration

When a donor enters in the system for the first time, he/she is requested to provide personal (e.g., name, address, age, job, gender) and medical/health (e.g., diagnosis, lab results, treatments) data, which are digitally collected. Digital registration provides a good traceability of the transfusion cycle, from collection to plasma distribution and transfusion. The registration also includes a visit from a physician, followed by plasma exams. If the donor is eligible, plasma collection centres check that he/she makes the first donation within few days from the declaration of eligibility. Sometimes, the first visit is directly followed by a donation. A visit is also made before each donation or exam, during which the donor is re-evaluated and his/her personal data are updated.

Several management problems arise, both at a planning level (e.g., plasma collection centre location or staff dimensioning) and at an operational level (e.g., appointment scheduling). However, only few papers focus on optimization issues arising in the registration and donation phase, despite the strong impact of donors' arrivals on the overall system performance. Michaels et al. (1993) developed a simulation study to evaluate scheduling strategies of donors arriving at a Red Cross plasma drive, and compared these strategies in terms of donors' mean transit time to find out the most effective one.

Other papers focus on estimating the supply of plasma from donations, considering annual donor retention rates, donor recruitment rates, and mean numbers of donations per donor and per year (Borkent-Raven et al. 2010). Ritika and Pau (2014) examined different classification algorithms to find out a fair classification technique for the prediction of donations. Flegel et al. (2000) developed a logistic regression model to compute the donation probability within a given time frame, considering different regression coefficients for walk-in and returning donors. Ferguson and Bibby (2002) used a prospective design to predict the number of future plasma donations. Boonyanusith and Jittamai (2012) investigated the pattern of donors' behaviors based on factors influencing plasma donation decision using a questionnaire.

Finally, on-line applications and database systems for donors' and bags manage- ment are also investigated (Chau et al. 2010; Khan and Qureshi 2009; Kulshreshtha and Maheshwari 2011).

**Plasma Collection and Screening**

Plasma collection centres should be located according to their accessibility from hospitals in order to improve the overall system performance. Moreover, centres are generally subject to regulatory control, designed to ensure the maximum quality and safety of plasma products. They guarantee that plasma bags are produced according to standardized procedures, to achieve consistency of each product (Council of Europe 2007).

Despite the importance of this phase, the literature on plasma collection system planning is rare (Ofori et al. 2005; WHO 2008; Lieshout-Krikke et al. 2013). De Angelis et al. (2003) proposed a stochastic methodology to analyse and certify the optimal configuration of servers by integrating simulation and optimization for a transfusion centre in Rome.

After collection, the screening phase starts with few tests performed against infectious diseases, e.g., HIV, Hepatitis B and C, and syphilis. They are repeated on each gathered plasma sample, and are generally the same all around the world. Based on screening results, the plasma bag is either released for clinical and manufacturing use or discarded (WHO 2008, 2010). An effective, well-organized screening program and a good quality system are essential for provisioning safe plasma bags to patients and meeting the transfusion requirements.

## Transportation and Storage of Plasma Products

Once collected from donors at regional or community plasma centres, plasma must be stored in storage centres or TC before it perishes. These locations serve as a depot until the plasma is distributed to the demand points and sometimes deal with testing of the plasma products.

If collection and storage or TC centres do not coincide, plasma must be transported. Although transportation is a rather simple task in this phase because all collected bags are usually addressed to a big TC or storage centre from all PD cen- tres in the related territory, transportation must be carefully performed as the plasma must be stored before perishing and requires particular transportation conditions. Inefficient and inadequate transportation may reduce the quality of end user care and increase costs. There is not much literature available about plasma transportation between collection and storage centres; on the contrary, many papers on plasma transportation focus on the distribution to hospitals (see subsection "Distribution and Utilization"). Ghandforoush and Sen (2010) used a deterministic non-convex integer optimization model to schedule the shuttle transportation of whole plasma products from the collection points to the regional processing centres.

The presence of plasma collection vehicles is also considered in plasma bag transportation. Ekici and Ozener (2014) defined a variant of the Vehicle Routing Problem, i.e., the Maximum Plasma Collection Problem (MBCP), in which plasma collected in a set of plasma donation sites is delivered with a fleet of collection vehicles to a single processing centre. Usually, there is no capacity limitation on the vehicles due to small size of the plasma collection bags (Yi 2003; Doerner et al. 2008). On the contrary, time constraints are important because donated plasma has to be delivered to the processing centre within a certain amount of time.

More attention has been paid to the storage of plasma products. During the past 20 years significant progresses have been made in the technology of plasma component preparation and storage (McCullough 2005; Blajchman et al. 1979). Belien and Forcé (2012) included several works in their survey.

Literature is mainly focused on inventory management problems (Padmanabhan and Vrat 1995; Axsäter 1996; Giri and Chaudhuri 1998; Dye and Ouyang 2005; Parlar et al. 2011), from both a deterministic (Padmanabhan and Vrat 1995; Axsäter 1996; Giri and Chaudhuri 1998; Jayaraman et al. 2010; Lieshout-Krikke et al. 2013) and a stochastic perspective (Prastacos 1978; Sirelson and Brodheim 1991; De Angelis et al. 2003; Pereira 2005; Katsaliaki 2008; Kopach et al. 2008; Blake 2009; Van Dijk et al. 2009; Parlar et al. 2011; Alfonso et al. 2012). Sirelson and Brodheim (1991) built a stochastic simulation model as a function of base stock levels to manage inventory level, outdated performance measures and shortage rates. Pereira (2005) built a stochastic model for a hospital plasma bank inventory system, in which the remaining shelf life of plasma units and the number of days between consecutive shipments were analysed according to the daily transfusion mean and variation impact.

Katsaliaki (2008) used a stochastic simulation model for a cost-effective management of plasma in the UK: valuable recommendations are provided to the stakeholders for cost reductions and for increasing the level of services and safety of the processes. Pierskalla and Roach (1972) grouped stock levels into categories according to shelf age; to satisfy the current (deterministic) demand, a First-In First- Out (FIFO) optimal policy was then applied issuing the oldest unit. Kopach et al. (2008) revisited a queuing model and, using level crossing techniques, determined an optimal policy to support the modeling of several trade-offs; the model was also combined with the current control techniques using simulation and the effectiveness of the model was verified with real data. Hemmelmayr et al. (2009) evaluated the impact of switching from their present vendee (customer) managed inventory system to a vendor (supplier) managed inventory system via a stochastic integer programming-based approach.

Some researchers extended inventory models like the Economic Order Quantity (EOQ) policy for including perishable products. For example, Giri and Chaudhuri (1998) proposed an inventory model for a perishable product where the demand rate is a function of the on-hand inventory, and the holding cost is non-linear. Padmanabhan and Vrat (1995) proposed a stock-dependent selling rate model where the backlogging function was assumed to be dependent on the amount of demand backlogged. Dye and Ouyang (2005) extended their model by introducing a time- proportional backlogging rate.

## Distribution and Utilization

The last step of the PD chain includes distribution and utilization, which involve several management problems as detailed below. Distribution is highly important for efficient plasma usage and should meet the demand, which is often uncertain and requires accurate predictions.

### Demand Prediction for Plasma Products

Several works include an evaluation of the demand, even if general papers that only focus on a stochastic prediction of the demand are not available. They can mainly classified based on the demand structure: deterministic (Pierskalla and Roach 1972; Prastacos and Brodheim 1980; Hirsch and Brodheim 1981; Hirsch and Cazal 1981; Sahin et al. 2007; Ghandforoush and Sen 2010) or stochastic (Kaspi and Perry 1983; Jagannathan and Sen 1991; Custer et al. 2005; Pereira 2005; Katsaliaki and Brailsford 2007; Sahin et al. 2007; Katsaliaki 2008; Kopach et al. 2008; Haijema et al. 2009; Van Dijk et al. 2009; Hemmelmayr et al. 2010; Delen et al. 2011). Moreover, some of the works can also be classified with respect to the aggregation level: single hospital (Novis et al. 2002; Pereira 2005; Katsaliaki 2008; Blake 2009; Haijema et al. 2009; Perera et al. 2009; Van Dijk et al. 2009; Delen et al. 2011) or regional level (Glynn et al. 2003; Bosnes et al. 2005; Carden and DelliFraine 2005; Denesiuk et al. 2006;

Katsaliaki and Brailsford 2007; Sahin et al. 2007; Erickson et al. 2008; Katsaliaki 2008; Kopach et al. 2008; Davis et al. 2009; Van Dijk et al. 2009; Hemmelmayr et al. 2009, 2010; Ghandforoush and Sen 2010).

Some peculiarities of the process are also considered. For example, Kaspi and Perry (1983) considered a system in which both arrival of plasma products and demand are modelled via stochastic process as independent Poisson processes. Silva Filho et al. (2012, 2013) developed a demand forecasting tool to make decisions about the weekly demand required by hospitals, and improved the planning of the inventory balance process with a strategy oriented to the forecasting of the demand of plasma components. Forecasting the monthly demand was also investigated in Pereira (2004) by univariate time-series methods. Lau et al. (2013) predicted the future plasma demand of thalassemia major patients for the next 10 years for long-term management of plasma supply.

**Management Policies**

Some papers deal with the decision making support in PD supply chain management, and on how to maintain or increase the supply of plasma products (Sahin et al. 2007; Davis et al. 2009; Haijema et al. 2009; Van Dijk et al. 2009; Ghandforoush and Sen 2010; Hemmelmayr et al. 2010; Delen et al. 2011). Sahin et al. (2007) established several deterministic mathematical models to solve the location problem of plasma services. Hemmelmayr et al. (2010) used an integer programming model to generate low costs and robust delivery routes for the supply of plasma products to hospitals from a plasma bank, and showed the impact of the uncertain demand on the resulting routes. Haijema et al. (2009) combined stochastic dynamic programming and simulation for the inventory management problem; the first approach is used to obtain optimal solutions, whereas the latter to investigate various what-if questions.

**Distribution to Users and Usage**

Distribution starts with the delivering of com- ponents to hospitals, where they are transfused into patients. TCs are usually responsible for the provisioning of plasma products to hospitals, and the delivered quantities are limited by the shelf-life of plasma products as well as by the holding capacity. Two types of plasma distribution systems were outlined by Hirsch and Cazal (1981): the reactive type, where the inventory level of the hospital is managed with respect to demand, and the predictive type, where the demand is fixed on schedule. Prastacos and Brodheim (1980) focused on a deterministic mathematical pro- gramming model, whose target is to streamline the distribution of the regional plasma resources while viewing plan commitments. It is characterized by a centralized man- agement of plasma rather than an individual hospitals management, pre-scheduled deliveries, and a distribution system in which plasma is rotated among the hospitals. Generally, redistributing the plasma among hospitals is equally important for preventing out dating.

## Discussion and Open Issues

Our analysis points out the high number of papers related to the management of storage and distribution phases. Indeed, Fig. 2 shows the percentage of the existing works for each phase. It can be seen that, even though the arrival of donors and the registration and donation system strongly affect the entire PD chain, only the 1 % of the investigations are devoted to improve these aspects. Hence, we found out the necessity of more adequate analyses and studies for this phase.

In particular, a relevant problem is the management of donors' appointments and visits, as it has a significant impact on the effectiveness of the entire PD chain and on donors' motivation. Increasing the number of donations improves the performance of the system, but also an effective management of donors' arrivals along with the days may optimize the daily production of bags with respect to the demand. Indeed, an unbalanced feeding of plasma bags undermines the entire PD chain; this is not only a theoretical problem, but from the discussion with several plasma providers this is the actual bottleneck of the entire system in the practice. Returning donors' appointments could be scheduled in advance, but not all donors are willing to accept pre-scheduled appointments, or they often require appointments at the beginning or at the ending of the day rather than at noon. Thus, an important future research is the development of optimization models and techniques for providing an efficient appointment scheduling, also in the light of balancing the production. The existing studies solved these problems by using simulation models (see, e.g., Lailomthong and Prichanont 2014); however, they do not fit the DB system since they do not take walk-in donors into account. The historical data collected by the PD centres can be exploited in these models, to forecast the walk-in donors' arrivals and increase the efficiency of the system. An effective application system is also needed in PD, as

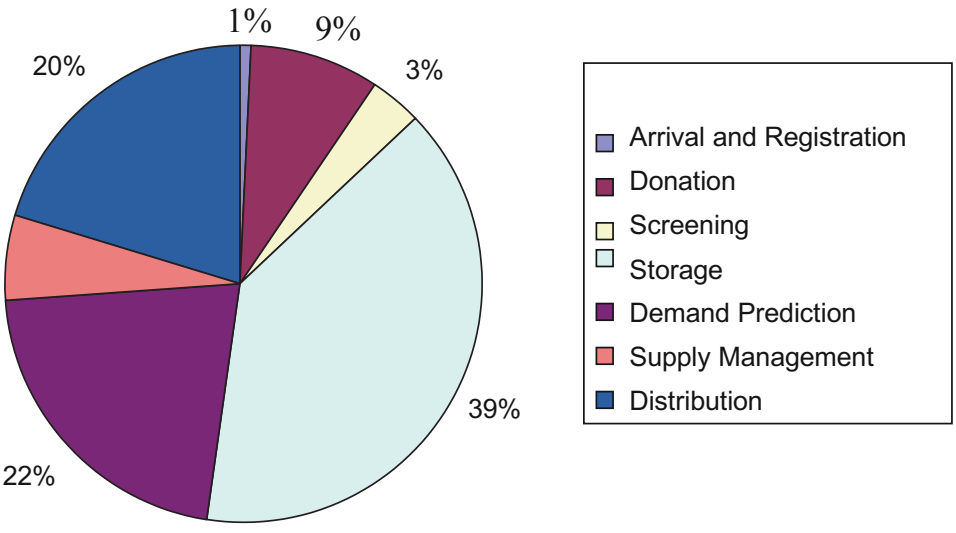


**Fig. 2** Percentage of the existing works for each phase

Percentage of the existing works for each phase , considering 156 papers on plasma management found in the literature (research updated at December 2014; papers on social and physiological aspect neglected) in other domains, to combine the registration system with donors' and physicians' preferences and their points of view. Such an application system (e.g., an on-line system) could be a solution to join donors and physicians at the same platform and to encourage volunteer donations.

Storage is another important step of the system. A successful storage manage- ment should guarantee a proper balancing between the plasma to hold and that to transfer, to keep plasma in optimal conditions and to avoid expiring and discharging. This also stresses the importance of an adequate feeding with respect to the demand. The storage problem is widely studied in the literature (the 39 % of the investigations in Fig. 2). Existing models are generally based on the analysis of the normalized stock level, and they aim at predicting and reducing outdated bags and plasma shortage. Nevertheless, an integrated management with plasma feeding, i.e., with donor appointment scheduling, might increase the efficiency of the whole PD chain and reduce both outdated bags and plasma shortage.

As mentioned, demand prediction is another crucial issue in PD system management. Inaccurate estimations of plasma demand may lead to disruptive consequences. For example, underestimation leads to low quality of the service, out-of-stock and additional expenses; on the other hand, overestimation leads to overproduction and overstocking, together with increased costs and clinical and ethical problems in throwing bags away. Demand variation is an important factor to which the entire process must properly react; for example, plasma inventory management becomes critical in case of increased demand, and the related decisions must be taken on time. However, meeting the demand is not easy since also the number of donors is difficult to foresee; hence, an integrated approach that considers the variation of both demand and donor arrivals should be required to better manage the PD chain.

Finally, transportation and delivery of plasma products are largely addressed by means of optimization tools. Generally, the existing works deal with the routing of delivery vehicles for the distribution of plasma components. As a future research line, with the increase in the use of plasma components, an emerging logistics problem is the distribution of different products, while taking into account both their different shelf lives and cost minimization (multi criteria objective).