# Clinical appropriateness of blood component transfusion: regulatory requirements and standards set by the Scientific Society in Italy

Giuliano Grazzini

*Centro Nazionale Sangue, Istituto Superiore di Sanità, Rome, Italy*

## Introduction

Decision-making in health care is strongly conditioned by the values of patients and providers, available resources, and information showing effectiveness/efficacy of a particular health care intervention. Clinical decisions concerning treating patients should, as far as possible, be evidence-based[1]; this is, to a great extent, the current clinical dogma, and many medical practitioners in all disciplines are now, to some extent, utilising it[2].

Evidence-based medicine (EBM) can be defined as the "*conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients*"[3]. It combines clinical judgment and experience with best available scientific evidence to improve medical decision-making and should provide clinicians, health care systems and policy-makers with instruments to appropriately evaluate the scientific evidence supporting various diagnostic and therapeutic activities. This represents a radical departure from the usual and customary methods for making treatment decisions concerning patients and has led to EBM being a discipline taught in medical schools and teaching hospitals[4]. Transfusion medicine (TM) is currently adopting the principles and research methodologies that support EBM[5], and high-level research has actually been undertaken at the same rate as in all medical specialties combined in terms of numbers of randomised controlled trials and meta-analyses[1].

EBM in TM not only refers to the best research evidence, but is often based on a broader range of inputs, including public expectations about transfusion safety and issues concerning the precautionary principle; this implies that the criteria for evaluating the efficacy and cost-effectiveness of interventions in TM may differ substantially from those used in other areas[6].

The increasing need to deliver sufficient and safe blood components of high quality may be the cause of an "*excessive focus on the supply side of the blood transfusion chain rather than the clinical problem facing patients and clinicians*"[7]. An overwhelming concentration on the blood supply can lead to the appropriate clinical utilisation of blood components being ignored as a potentially useful instrument to maintain the blood supply itself, although physicians should always consider clinical appropriateness as a *must*, under professional, scientific and ethical points of view. Hence, "*the appropriateness of transfusion practices will only improve, not by expecting clinicians to be gatekeepers of the blood supply, but with better patient blood management based on a sound understanding of pathophysiology and better evidence for transfusion efficacy*"[7].

Based on the above considerations, appropriateness of transfusion practices should systematically mean that blood components are transfused only when there is evidence for potential benefit, there are no valid alternatives, safe and quality products are available, and risks and benefits are carefully assessed before the decision to transfuse is made.

Recent European regulatory acts in the field of blood transfusion (Directive of the Council 2002/98/EC[8] and Directives of the Commission 2005/61/EC[9] and 2005/62/EC[10]), while focusing on fundamental issues concerning quality, safety, traceability, haemovigilance, etc., do not actually take into consideration the promotion and assessment of appropriateness of clinical use of blood components[11]. Indeed, the Community's legislative framework



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excludes the actual therapeutic use of blood components. Moreover, its provisions are no longer applicable when the components are sent for further processing into medicinal products, when pharmaceutical legislation comes into force[12].

The appropriateness of the clinical use of blood components is addressed by Recommendation Rec(2002)11[13], which is indeed an excellent guideline to member states on *how* and *what* to do to implement optimal use of blood and blood products in the clinical setting, but no mandatory act at the European level establishes that appropriateness of transfusion practices *must* be promoted, monitored, assessed and, when necessary, improved.

This review is aimed at providing an overview of the Italian regulatory framework and of the requirements of the Italian standards of TM on the assessment of the appropriateness of blood transfusion.

## Regulatory requirements on the assessment of the appropriateness of transfusion practices in Italy

In Italy, Blood Transfusion Centres (BTC) are, by law, only public, hospital-based services, mostly organised in departments and regionally co-ordinated. Regional Blood Centres are co-ordinated by the very recently instituted National Blood Centre.

BTC are entrusted with the management of the whole process of blood collection and transfusion, excluding bedside procedures performed outside the BTC themselves. They also manage several other activities, both diagnostic and clinical, related to TM in the hospital and in the outpatient setting, such as therapeutic apheresis, transplantation immunology, tissue and cell banking, etc.

A "*New discipline for blood transfusion activities and national production of blood derivatives*" was implemented in Italy in 2005, by the 21 October 2005 national law[14]. The fundamental aims of this law are:

a) regional and national blood and blood product self-sufficiency;
b) implementation of high quality and safety standards throughout the whole process of blood collection and transfusion;
c) delivery of homogeneous health care services in TM nationwide;
d) technical and scientific development of TM;
e) appropriate utilisation of blood resources;
f) specific transfusion programmes in haematology, oncology, emergency care and transplantation.

National "*essential transfusion medicine healthcare services*" (ETMS) are established in detail by the law. They must be homogeneously guaranteed nationwide by the regional health authorities through their BTC.

ETMS are classified into "productive" and "clinical" services, the latter specifically including the *assessment of the appropriateness of blood transfusion practices*.

The law establishes that appropriate transfusion practices must be promoted and applied nationwide, through the activity of hospital transfusion committees (HTC), which must operate in each public health trust, with the objective of implementing programmes on blood and blood product utilisation, audits, corrective and preventive actions and improvement plans.

HTC have been regulated by a Decree of the Ministry of Health since 1995[15].

This Decree established the institution, composition and tasks of HTC. Most of the concepts concerning appropriate use of blood and blood products were fixed in this Decree, which defined *what* to do, leaving *how* and *who* more indefinite. According to a recent survey promoted by the Italian National Blood Centre, HTC have actually been instituted in about 95 per cent of public hospitals and are actively working in 70-75 per cent of them (data not shown). The functioning HTC play a pivotal role in ensuring the appropriate use of blood products by developing local transfusion policies, procedures and guidelines, properly implementing autologous transfusion, educating clinicians and auditing blood use.

According to the 2005 blood law, all institutional bodies (Ministry of Health, National Blood Centre, regional health care authorities, BTC and HTC), according to their respective roles, are involved in specific goals aimed at promoting, monitoring, assessing and auditing the appropriateness of the clinical use of blood components. The Ministry of Health, the National Blood Centre and regional health care authorities should also promote scientific research on the optimal use of blood. Moreover, the new national blood information system (SISTRA), currently being implemented, shall collect adequate information on the appropriateness of transfusion practices, and provide data to enable scientific and cost-effectiveness evaluations.

Finally, another important national provision, the Decree of 3 March 2005 of the Ministry of Health[16], updating preceding national regulatory acts and transposing Commission Directive 2004/33/EC[17], establishes that blood components for transfusion can be requested only by a physician and that BTC must have a standard operative procedure (SOP) in place to assess the appropriateness of blood component requests; the assessment must be performed by a TM physician.

The specific assessment task attributed to BTC and systematic auditing by HTC should allow documentation of local, regional and national rates of appropriateness of blood component transfusion. A very important challenge for Regional Blood Centres and the National Blood Centre will be to collect relevant information on this issue and make it systematically available to the interested stakeholders.

## Standards of the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI)

In September 2007, SIMTI edited the *Standards of Transfusion Medicine*[18], in accordance with the decision of the Scientific Society's national board to provide a voluntary reference instrument for the Italian TM community. The Standards are focused predominantly on technical and professional issues, although comprehensively include organisational and management aspects.

The Standards were also issued to comply with the Society's mission, which states that SIMTI shall "*offer the decisional and advisory organs of the State, Regions and Institutes involved in the field of transfusion and immunohaematology expert collaboration in the planning and development of the transfusion service in the country*"[19].

The Standards deal with all principal issues of TM and are conceived so as to comply with the organisation of the Italian blood system, which entrusts BTC with a wide range of functions, including several clinical tasks. Hence, all the fundamental clinical services that BTC must provide are covered.

Chapter D of the Standards deals with *individual attribution and release of allogeneic blood components*, setting requirements for the appropriate and safe management of the whole transfusion process, from information to be supplied to physicians entitled to request blood components to basic haemovigilance procedures.

Assessment of the appropriateness of blood component requests and clinical TM counselling, both to be performed by BTC physicians, are dealt with in detail in Chapter D.3 of the Standards. The essential contents are reported below.

- Formally approved guidelines for the optimal use of blood components shall be adopted by BTC to perform the assessment of appropriateness, which should also rely on BTC physicians' continuous education and upgrading of specific clinical skills.
- Guidelines shall be preliminarily shared with the main blood users; it is recommended they are approved in the HTC, and formally diffused by hospitals' executives.
- Specific requirements are set concerning the contents and quality of guidelines, including criteria for effective searches of scientific literature and the critical appraisal of scientific evidence.
- It is recommended that guidelines include clinical indications for the main plasma-derived products (albumin, aspecific intravenous immune globulins, prothrombin complex concentrate, and antithrombin).
- Guidelines shall be periodically revised to incorporate scientific progress.
- All routine requests for blood components shall be systematically assessed by a BTC physician. Emergency requests shall also be assessed, provided the clinical conditions of involved patients allow the necessary time; otherwise, the requests shall be audited retrospectively.
- A blood component request is classified as inappropriate in the case that it has to be qualitatively and/or quantitatively modified after the BTC physician's prospective assessment, or retrospective audit.
- In the case of lack of agreement between the BTC physician and the requesting physician, it is recommended that the BTC physician's opinion be formally notified to the head of the ward or clinic in which the patient is being cared for and to the chairman of the HTC. The blood components should, however, be released.
- All assessment and counselling activities shall be documented.
- BTC are also responsible for systematic collection of data on assessment activities and TM counselling, and for relevant statistical analyses, to be periodically reported to the HTC, where data



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shall be evaluated in order to implement corrective and preventive actions and improvement plans, whenever necessary.

Finally, it is important to remember that the requirements and recommendations described in this paragraph are part of a voluntary system of standards.

## Conclusions

In Italy there has been a significant degree of attention to the appropriateness of transfusion practices since the early 1990s, when the first national guidelines were issued promoting a "*reduction*" of allogeneic blood transfusion[20].

New national legislative provisions have confirmed the existing organisational model of the blood system, centred on hospital-based BTC, although enhancing the implementation of regional rationalisation processes aimed at consolidating blood component production and biological qualification in a few centres.

Promotion, control and improvement of appropriateness of transfusion practices are diffused nationwide through specific regulatory provisions, establishing the accountability of both blood component users and BTC as well as TM physicians, the latter carrying out, by law, the role of "guarantors" of the appropriateness of blood component transfusion. This concept has been confirmed and strongly empowered by the Standards produced by SIMTI.

Mandatory clinical assessment by TM physicians in the attribution of blood components to patients, performed in the unitary framework of BTC, intended as specialised hospital services, is supposed to have contributed significantly to maintaining average red blood cell (RBC) consumption° in Italy around 42 units/1000 population/year (41‰ in 2006, 41.4‰ in 2007, and an estimated 42.4‰ in 2008). With these consumption rates all appropriate transfusion needs are satisfied in Italy, a country with about 58.7 million inhabitants and with average health care needs that are at least the same as those of socio-economically comparable European countries, if not greater, due to the huge number of patients affected by congenital blood disorders, such as thalassaemia.

The appropriate clinical governance of RBC consumption is now an absolutely essential part of maintaining national self-sufficiency which - for 2008 - has been estimated to require a national production of around 43 units/1000 population[22].

According to institutional data[21,22], in some Italian Regions in which the attribution and release of RBC are partly delegated to hospital services not directly or entirely managed by BTC, RBC consumption is significantly higher (>50‰) than the national average; this is supposed to be independent of clinical complexity (case mix) and of the number of non-resident patients treated. Extensive benchmark studies based on associations between specific diseases (classified by the ICD9-CM system[23]) and blood component transfusion should be conducted in order to provide solid evidence to clarify these phenomena, while at the same making data available to update guidelines and, possibly, regional and national regulations.

Over the past 20 years, scientific progress, the development of new technologies, increasing demand for blood products, widespread concern about maintaining the blood supply, increasing quality and safety requirements for products and services, together with greater public awareness of transfusion risks, economic constraints and more stringent regulatory provisions, have dramatically changed TM and, perhaps, some substantial aspects of the profiles of professionals working in blood systems.

Will these changes increasingly imply a shift of TM towards a "pharmaceutical" destiny? Will it be possible to maintain adequate blood and blood product supplies if *appropriate needs* do not replace what, maybe too often, is the *demand* for blood components? Will TM physicians become excellent "technologists" working according to SOP, but wrenched away from clinical issues?

We agree with Isbister[7] that clinicians should not be expected to be the *gatekeepers* of blood supply, but at the same time we believe that there are valuable reasons to affirm that TM physicians should be the gatekeepers of clinical appropriateness of transfusion practices.

European haemovigilance studies have shown that patients still run significant risks resulting from failures in the therapeutic use of blood components. While collection, testing, processing and distribution of blood and blood components have been regulated and must meet mandatory standards, we agree with Robinson[11] that there is now a call for the development of European-wide measures to ensure appropriate use

° The consumption rate includes about 4% of red blood cell units produced which are discarded for various reasons (non-compliance with standards, outdating, etc).

of this vital but increasingly costly and limited resource.

It is to be hoped that the forthcoming regulatory acts in Italy, applying the 21 October Law and European Directives regarding BTC authorisation and accreditation and national blood policies, will be coherent with these issues.

**Key words:** appropriateness, blood transfusion, blood components, transfusion medicine standard, regulatory requirements.

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Correspondance: Dr. Giuliano Grazzini,
Centro Nazionale Sangue, Istituto Superiore di Sanità,
Via Giano della Bella, 27
00162 Roma, Italy
e-mail: giuliano.grazzini@iss.it


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