the hemostatic system activation. This also expands our vision of the possible mechanism(s) involved in the hemolytic crisis brought on by other comorbid conditions, such as sepsis. Along the same lines, there is evidence that the HbF levels, an important regulatory mechanism of SCA severity and hemolysis, govern MP concentration by acting on specific MP subtypes.

We can imagine that, in SCA children, a storm of various (mainly platelet-derived) procoagulant MPs takes place with chronic hemolysis and is driven by HbF levels (Figure 1).

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Are ongoing trials on hematologic malignancies still excluding older subjects?

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Hematologic malignancies are diseases that mainly affect older subjects. Multiple myeloma,[1] myelodysplastic syndromes[2] and chronic myeloid leukemia[3] are common in advanced age. Nevertheless, there is evidence that older patients with hematologic malignancies have often been excluded from clinical trials (CTs).[4,5] Their exclusion prevents clinicians from obtaining information concerning the efficacy and safety of treatments in older patients and might represent an important barrier to the treatment of these patients.[6] Published literature reflects trials performed some years before their publication. It is not known whether older individuals are gradually being included in more trials as a consequence of the aging of the population and of the recommendation provided by Regulatory Agencies, e.g. FDA and ICH, to include older individuals in CTs.[7,8] The aims of this study were to assess the presence and the extent of underrepresentation of older individuals in ongoing CTs on hematologic malignancies registered in an online open-access CT registry maintained by the World Health Organization (WHO), and to evaluate

the relationship between eligibility criteria and trial characteristics.

Information regarding ongoing CTs was obtained from the WHO International Clinical Trials Registry Platform (WHO-ICTRP).[9] This database collects trials registered in the Australian New Zealand Clinical Trials Registry, the International Standard Randomized Controlled Trial Number Register, the US Food and Drug Administration Registry, the Netherlands Trials Registry, the Chinese Clinical Trials Registry, and the Japan Primary Registries Network. A search was performed using the following keywords: "cancer" OR "tumor" OR "neoplasm" OR "malignancy", in the condition field; "all" in the register field; and "recruiting" in the recruitment field. We identified the most relevant information to collect from the study protocol of each CT. The methodology was adapted from that used in the PREDICT study.[10] We classified hematologic malignancies based on 2008 WHO classification.[11] Concerning exclusion criteria, we assessed the presence of an upper age limit (explicit exclusion) and other exclusion criteria (implicit criteria) that might potentially lead to a reduction in the number of older individuals included in the trials, such as exclusion by comorbidity, cognitive or physical impairment, reduced life expectancy, pharmacological therapy, visual or hearing deficits, or inability to attend the follow up appointments.

Descriptive statistics have been performed for discrete and continuous variables. The analysis of contingency tables for categorical variables was supported by Pearson's χ^2 test or Fisher's exact test for sparse tables or for tables larger than 2 × 2. Univariable logistical regression models were used to identify variables more associated with the specific cause of exclusion on the basis of χ^2 Wald statistics ($P>\chi^2$ Wald <=0.25). A linearity study was performed for continuous variables and transformations have been applied when necessary. Any variable whose univariable test has $P<0.25$ has been chosen as a candidate for the multivariable logistical regression models. Multivariable logistical regression model computation with automatic selection of the best model (backward and stepwise methods) has been performed to discover variables significantly associated with each cause of exclusion using SAS software (version 9.2, SAS Institute Inc., Cary, NC, USA).

As of February 3rd, 2011, there were 9074 registered trials recruiting patients with cancer in the WHO-ICTRP. A total of 8807 studies were excluded because they investigated solid tumors. From the remaining 267 CTs, 182 were excluded for the following reasons: 106 were phase I studies, which might reasonably exclude older patients considering their highly experimental nature, 9 because of their observational design, 6 because they involved children, 14 because cancer was not the main target condition (e.g. graft-*versus*-host disease), 10 because the primary purpose was not treatment, 33 because they adopted a high-dose radiation protocol which is not recommended in older subjects, 3 because they were pilot studies, and 2 because they were

Table 1. Characteristics of ongoing clinical trials regarding hematologic cancer in older patients (n=85)*.

Characteristics	Frequency, N (%)^
Design	
Randomized controlled trial	8 (9.42%)
Study phase	
II	79 (92.9%)
III	6 (7.1%)
Setting*	
Multicenter	37 (45.6%)
Unicenter	46 (55.4%)
Co-ordinating country	
Europe	15 (17.6%)
USA	61 (71.8%)
Other	9 (10.6%)
Sponsor	
Academic center	40 (47.0%)
Public funding agency	21 (24.7%)
Non-academic hospital	18 (21.2%)
Pharmaceutical industry	6 (7.1%)
Sample size median, (IQ range)	55 (40-100)
Duration (months) median, (IQ range)	46 (24-69)
Condition	
Hematologic cancer only	77 (90.6%)
Hematologic and solid cancers	8 (9.4%)
Intervention	
Drug	41 (48.2%)
Biological agent	12 (14.1%)
Procedure	7 (8.2%)
Combined interventions	25 (29.4%)

When the total number of a category is lower than 85 this is due to missing data, which belong to Japanese trials that did not provide the information in English. ^Unless otherwise specified.

Table 2. Frequencies of exclusion criteria that might negatively affect the inclusion of older individuals in ongoing clinical trials regarding hematologic malignancies.

Exclusion criterion	Frequency, N. (%)
Upper age limit	35 (41.18)
Reduced life expectancy	23 (27.06)
Drug therapy (at least one drug)	53 (62.35)
Abnormal laboratory result (at least one)	69 (81.18)
Cognitive impairment	5 (5.88)
Physical disability	62 (72.94)
Inability to give informed consent	32 (37.65)
Inability to attend follow-up visit	5 (5.88)
Physician's judgement	23 (27.06)
Reduced compliance	28 (32.94)
Comorbidity (at least one disease)	77 (90.59)
Specific disease	
Renal failure	60 (70.6)
Cardiovascular	56 (65.9)
Infectious	47 (56.6)
Hematologic	39 (45.9)
Lung	33 (38.3)
Psychiatric	31 (36.5)
Previous cancer	18 (21.2)
Gastrointestinal	17 (20)
Neurological	15 (17.6)
Liver	8 (9.6)

registered twice. Our analysis focused on 85 CTs. The main characteristics are described in Table 1. The majority of CTs (75.9%) were registered in the USA registry. Most CTs planned to enroll patients with different types of hematologic malignancies (53%). The most common malignancies were mature B-cell cancer (74%), acute myeloid leukemia (33%), myelodysplastic syndromes (30.5%), Hodgkin's lymphoma (26%), and myeloproliferative neoplasms (26%). The frequencies of exclusion criteria are given in Table 2. The most common exclusion criteria were the presence of at least one comorbidity (91%), at least one abnormal laboratory result (81%), the use of one or more specific drugs (67%), and upper age limit (41%). The mean upper age limit was 68 years (SD 8.3). Univariable analysis showed that a longer duration of the trial and specific blood malignancies (leukemia, myeloproliferative and myelodysplastic syndromes) were associated with exclusion because of upper age limit. Moreover, if the trial promoter was an academic center, there was the highest probability of exclusion for upper age limit (P<0.03). In the logistical model, only a longer duration of the trial remained significantly associated. An upper age limit was an exclusion criterion in 52% of the trials registered before 2008 (n=21) compared to 31% in those registered after 2008 (n=14; P<0.05).

The main finding of our study is that older patients are still commonly excluded from CTs on hematologic malignancies. The age cut off is in the majority of CTs is below 70 years, an age at which the risk of several hematologic malignancies increases.[1,2] This threshold is also below the average life expectancy in industrialized countries: at 70 years of age the majority of subjects are still independent or with only minor problems with the more complex activities of daily living. The paucity of data on treatment efficacy and safety is likely to contribute to the high rate of undertreatment of cancer patients,[12,13] including those with hematologic malignancies.[14] This is also suggested by the fact that novel agents have been shown to improve the outcome of younger patients with multiple myeloma and to be effective also in older patients,[15-17] but very little progress has been achieved in survival in the latter group.[18,19] Moreover, the toxicity and the outcome of autologous stem cell transplant in selected older patients appear comparable to those in younger patients.[20]

All this leads us to conclude that the exclusion of older subjects is inappropriate and more elderly individuals should be enrolled in CTs. Although recent years has seen a fall in the percentage of trials with age as exclusion criterion, this does not guarantee that older patients will be included in CTs. Ongoing trials have a multiplicity of exclusion criteria that could limit the participation of older patients, in particular concomitant diseases and pharmacological therapies. Our study has some limitations. First, our analysis was restricted to the WHO-ICTRP registry, which is not necessarily representative of the ongoing trials worldwide, e.g. at the time when data were downloaded from the database the European database of CTs was not included. Moreover, we examined only eligibility criteria and we cannot know the characteristics of the sample that will be finally enrolled.

The increasing number of older subjects aging in better clinical condition will necessarily require a change in this persistent form of age-related discrimination.

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A European strategy for targeted education in hematology

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Developing the evidence base: the H-Net project

As described in previous editions of *Haematologica*, the European Hematology Association was the lead partner in the European Union (EU)-funded project H-Net 2008-2011. The goal of the H-Net project was a harmonized curriculum for European hematologists as expressed through the document called the CV Passport,[1] developed in 2006 within a previous project and revised in 2011. The existence of this agreed curriculum enabled the EHA and its partners in the H-Net project to move forward in identifying training needs and gaps (whether on an individual, national or European-wide basis), and thus to improve strategic planning of educational provision and resources.

Within the H-Net project, a key first step was the implementation of a survey based on the 2006 CV Passport.[2] Data from the survey, national figures and European graphs for comparison were reported back to the national societies through the H-Net linkers and the societies were requested to consider these and to produce Preliminary Strategy Reports. These reports were extremely helpful in interpreting the survey findings. Not all data were robust on a national level due to small sample sizes or insufficient information on the nature of the sample. The national societies recognized this, but nevertheless they were able to comment on trends and indications in relation to their knowledge of national curriculum practices and organization of care for hematology patients, and, in many cases, to offer a valuable interpretation of the survey findings. This additional information enabled the H-Net project team to confirm some findings from the survey and to treat others with caution.

European-wide findings

The final step before the compilation of a general strategy document was to examine the entire dataset to identify strengths and gaps on a European level, comparing these when possible with regional data. All items were identified for which 50% or under of respondents assessed themselves as being at the competence level recommended in the CV Passport, and, similarly, all those items for which 30% or under made this assessment. These items were carefully scrutinized by an experienced hematologist to see if any possible explanations suggested themselves. For example, in the *Clinical Hematology* section of the CV Passport, most deficits were seen in the context of:

- rare conditions normally handled by pediatricians/pediatric-hematologists;
- rare conditions normally referred to obstetricians/gynecologists;
- items commonly referred to departments of genetics;
- conditions with considerable variation in geographical occurrence.

This filtering allowed for the following items to be identified as potential educational priorities: spherocytosis and deficiency of G6PD, acquired platelet function disorders, interpretation of results of genetic and molecular biology tests.

Similarly, for the *Diagnostics* section of the CV Passport, the items identified as potential priorities were: morphology skills, interpretation of trephine bone marrow biopsy, sickling process, examination for RBC parasites, general principles of disease-oriented antibody panels, major genetic features in hematologic diseases.

For the *Thrombosis and Hemostasis* section, the items were: familiarity with staff performance management and appraisal, advising on use of blood products, taking a relevant case history, management of thrombotic thrombocytopenic purpura, interpretation of screening tests for primary hemostasis, clinical/laboratory tests for antiphospholipid antibodies, use of D-dimer assay and imaging, and diagnosis/management of heparin-induced thrombocytopenia. For the *Transfusion* section, there was only one item identified regarding autoimmune hemolytic ane-