Viral inactivated cryoprecipitate: A Global Initiative

on behalf of ALH (Luxembourg Hemophilia Association)

Dr Jean-Claude Faber, president; e-mail: jean.claude.faber@sfr.lu

No conflict of interest to disclose.

10th WFH GLOBAL FORUM
on Research and Treatment Products for Bleeding Disorders

WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Background and starting point for the Global Initiative

WFH: "Treatment for All" (since the beginning of 2000s).

WFH is strongly recommending use of **"clotting factor concentrates (CFC)".**

Declared goals should be achieved through **"product donations and advocacy".**
Resource limited countries are assisted with products donated by industry through WFH Humanitarian Aid Program and its advocacy skills and experience.

75-80% of all PWH have ***no*** access to ***any*** form of (effective) treatment – ***unchanged*** for past 20 to 30 years.

If treatment exists in developing countries (l-HDI), in most places it is RICE (rest, ice, compression, extension) and "native" cryo.

Supplies and inhibitors continue to pose important threats for PWH and remain unsolved problems in l-HDI .

Recent developments

Experience of the past 20-30 years has shown that **clotting factor concentrates (CFC) alone cannot solve persisting problems with hemophilia A treatment in developing countries (low-HDI).**

Recently, significant developments have occurred:

1. **blood systems** (in particular, blood centers) in many l-HDI have improved;
2. **technologies for viral inactivation (VI)** of blood components are available (amotosalen, riboflavin, solvent-detergent SD,…).

Combining progress and plasma availability, it is possible to prepare “native” cryo and to render it safe with pathogen reduction techniques, resulting in viral inactivated cryoprecipitate: Cryo-VI.

In several l-HDI, local preparation of viral inactivated cryoprecipitate has been introduced (using solvent-detergent and filtration, SD/F)*.

Cryo-SD/F has proven to be a safe and effective therapeutic for patients with bleeding disorders, at an affordable cost.

Local products from **existing blood centres** in l-HDI: safe&effective

Whole blood donations

Centrifugation of whole blood

Separation of different blood layers for blood component production

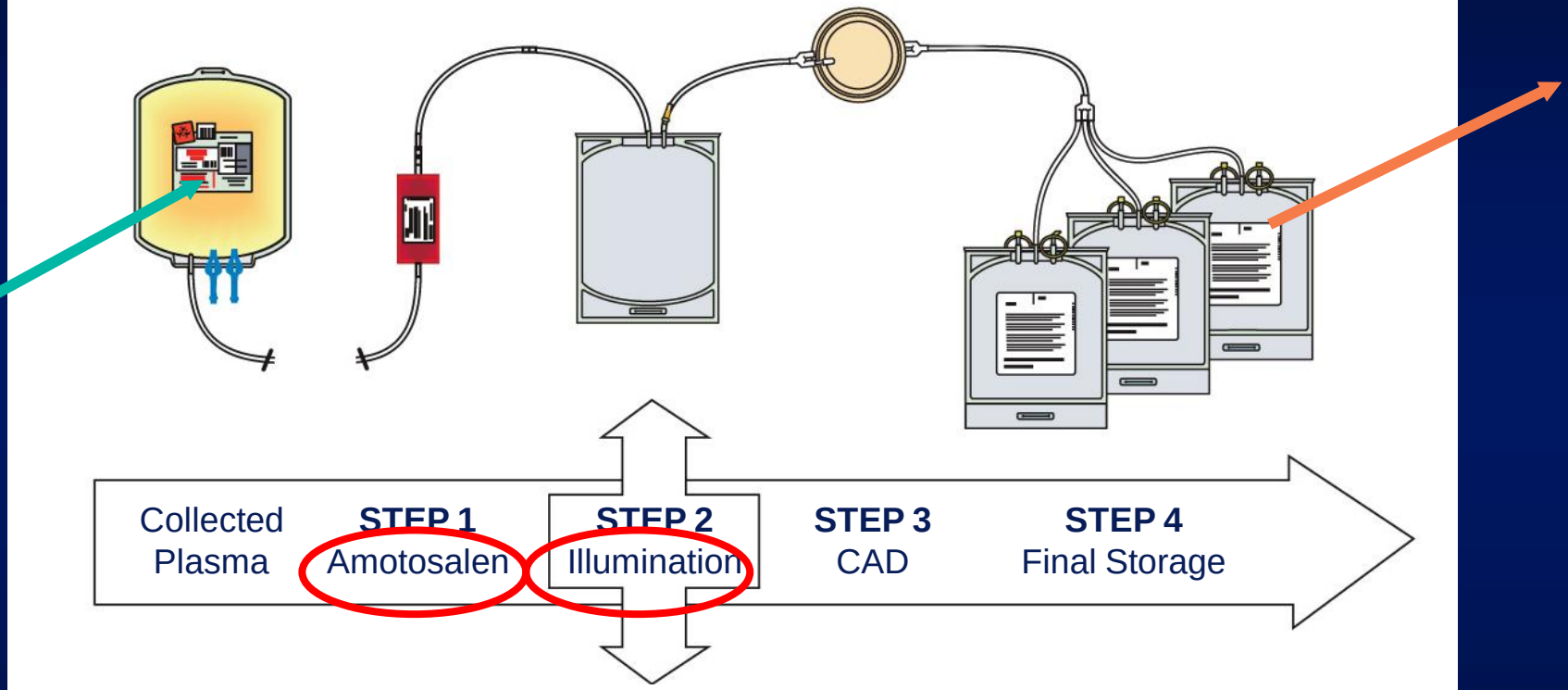
Release of finished blood components, incl. native cryo

One additional step: viral inactivation

Safe cryo

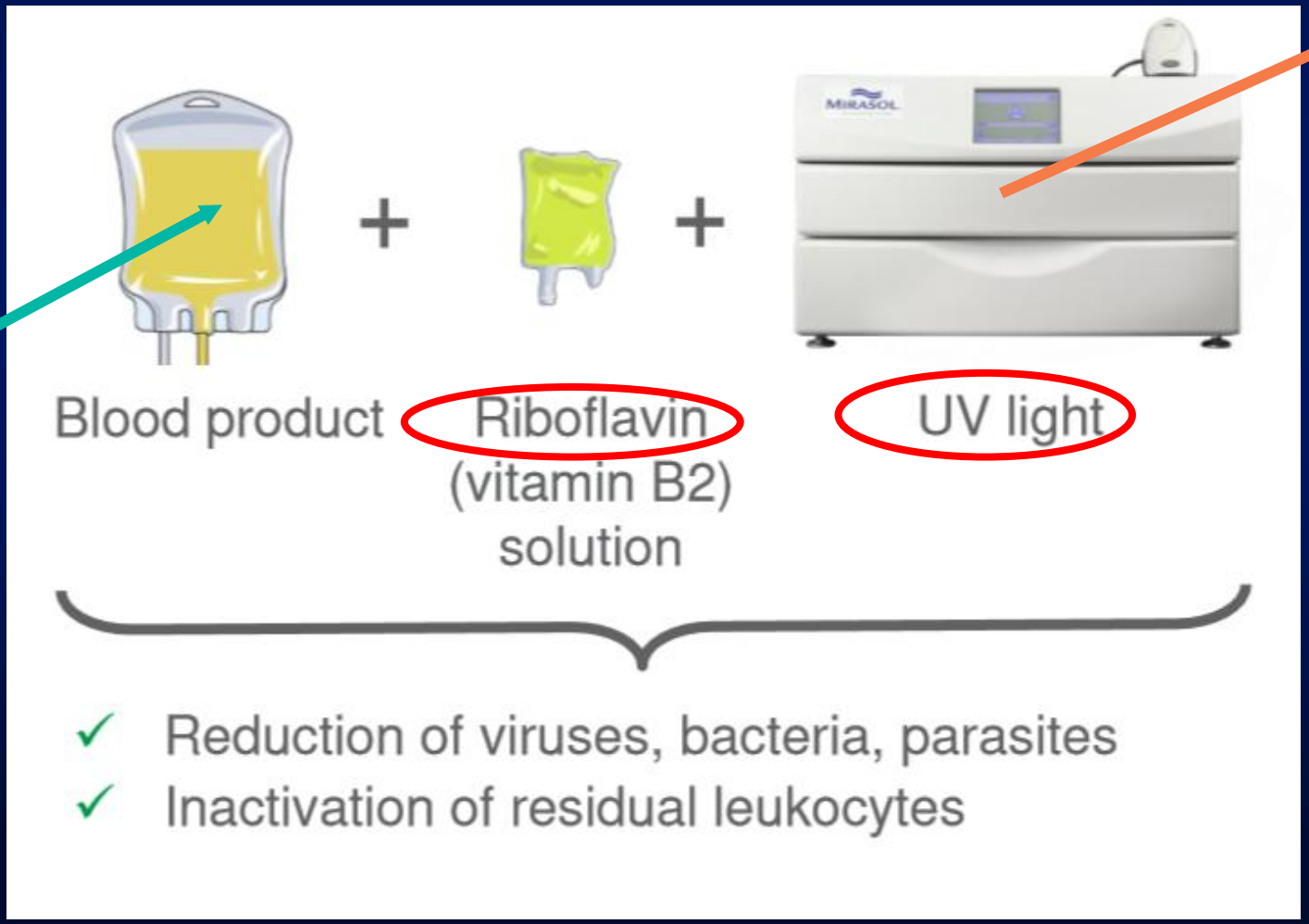
INTERCEPT® by **Cerus**:
approved and licensed for **plasma&platelets**

PMA supplement submitted to FDA for ***cryo*** *(p.r. July 27, 2017)*



MIRASOL® system by **TerumoBCT**: approved and licensed for **plasma&platelets**

validation & marketing authorisation ***to be undertaken for*** ***cryo***
(ongoing research on VI of WB, whole blood)



CRYO-SD/F® system by **VIPS**:
approved and licensed for **cryoprecipitate** (&**plasma)**

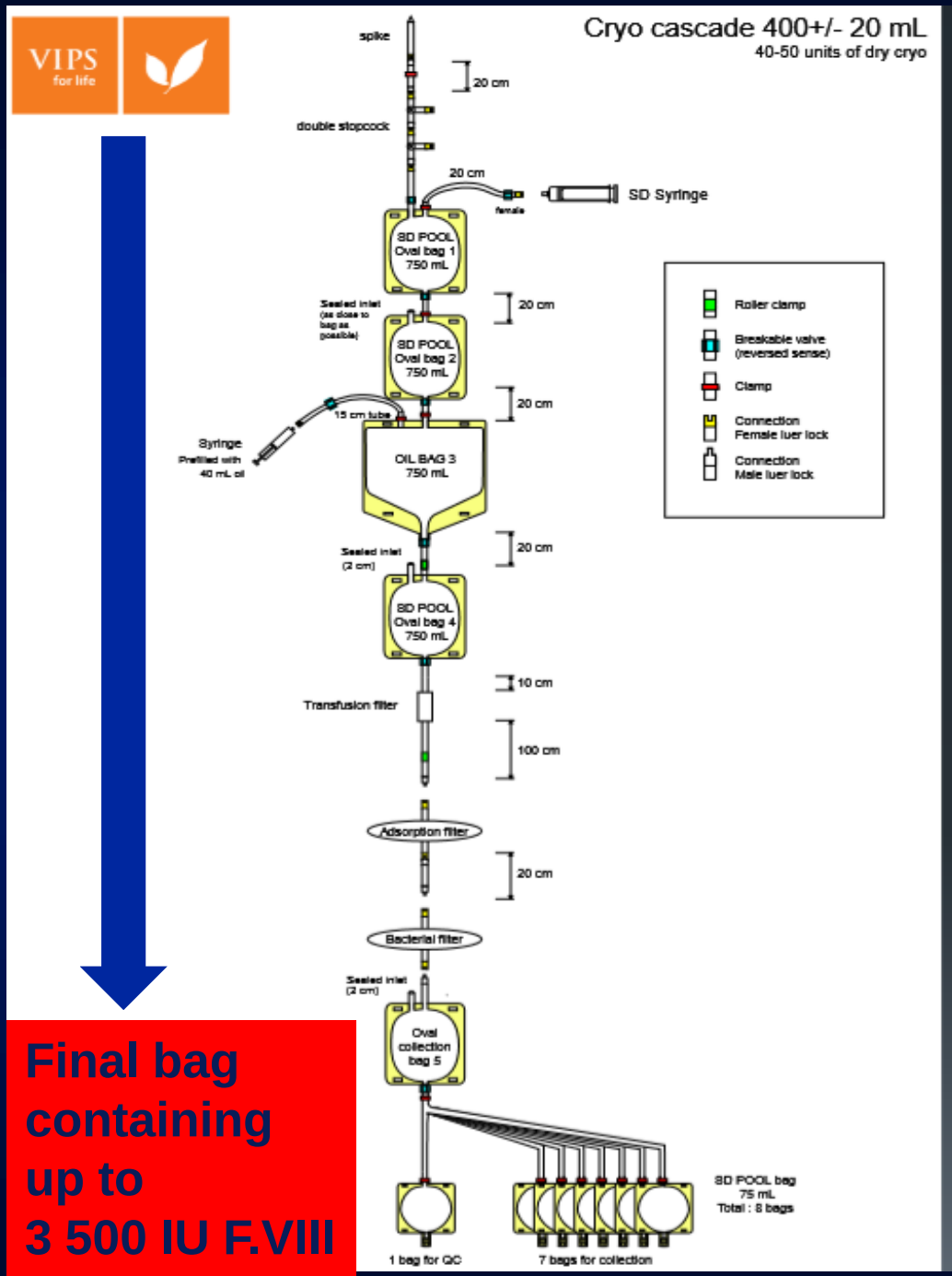
medical device
for safe cryo

using technology
based on SD/F

developed and
manufactured
by VIPS

approved by
Swissmedic,CH

marketed since
2010



Final bag containing up to 3 500 IU F.VIII

Pool 30-35 native «dry» cryos

Add solvent-detergent SD: TnBP and Triton X45

Mix carefully 2x

Add oil

Remove/extract SD with oil

Pass through absorption filter

«Sterilize» with bacterial filter

Condition into smaller portions

Viral validation studies

- Texcell/Pasteur Institute (France)
- Conducted following CPMP/EMEA guidelines
- Worst case conditions (low % range of SD, low temperature; no transfer to second viral inactivation bag)
- >4 log reduction of HBV, HCV & HIV virus models in cryoprecipitate (as well as FFP, and cryo-poor plasma) in two minutes

Comprehensive and global initiative

Taking into account, **persisting supply situations in developing countries**, unbroken "status quo ante", limited use of new technologies, absence of major actions to take advantage of recent developments,… ALH has come to the conclusion that a **global initiative** was needed to promote **local preparation of viral inactivated cryoprecipitate in developing countries,** to facilitate implementation and sustainability of an alternative strategy (*LP of Cryo-VI in l-HDI*).

End of 2016, a worldwide movement was launched to promote local preparation of safe cryo to treat patients with bleeding disorders in l-HDI. It is a **collaborative initiative with *international* partnering organizations** (WHO, ISBT and others, ?WFH) and ***national* stakeholders in developing countries** (competent authorities, blood services, medical community, patient organisations,...).

Global Initiative on "*LP of Cryo-VI in l-HDI*"

The 6 core interventions:

1. Revise, update standards&guidelines on hemophilia treatment and include *Cryo-VI*;
2. give high priority in relevant policies and strategies for *LP of Cryo-VI in l-HDI;*
3. advocate and promote *LP of Cryo-VI in l-HDI*;
4. run a pilot project on *LP of Cryo-VI in l-HDI*;
5. establish an expansion programme for *LP of Cryo-VI in l-HDI*;
6. contribute to activities for sustainability of *LP of Cryo-VI in l-HDI*,

supported by several **additional flanking activities.**

Global Initiative on "*LP of Cryo-VI in l-HDI*" (intervention 1.)

1. revise and update standards and guidelines on "anti-hemophilic" therapies:

multiple S&G exist, from many different organisations

national S&G often "follow" international (e.g. WFH, 2nd edition, 2012)

S&G from international organisations should:

- permit a realistic approach (feasibility, implementability and sustainability)
- give particular attention and focus to developing countries
- allow tailoring to country situations (taking into account capabilities and capacities of developing countries: dual set of doses, dual set of products)
- be in-line with policies and strategies on "hemophilia treatment"
- be updated regularly at short intervals (scientific and industrial progress, changes in the field are rapid)
- have pragmatic stratification according to groups of countries, treatment schemes, therapeutic products, dosage, health care delivery models,…

Global Initiative on "*LP of Cryo-VI in l-HDI*" (intervention 1.)

S&G should have pragmatic stratification for:

- categories of *countries* (there are considerable differences between jurisdictions in developed and developing world, with such an amplitude that one single set of principles can not serve them all adequately);
- groups of *patients* (there are individuals with *inherited* bleeding disorders like hemophilia, VWD and fibrinogen abnormalities, but also those with *acquired* bleeding disorders like fibrinogen consumption/depletion in women with complicated child delivery resulting in impaired hemostasis, maternal mortality);
- classes of ***products*** (clotting factor concentrates and other hemostatic products, including pathogen reduced blood products respectively viral inactivated blood components such as Cryo-VI);
- sub-classes of *medicinal products* (plasma-derived and recombinant; with full-length, B-domain deleted and fusion clotting factors, etc…)
- types of treatment *protocols* (prophylactic/continuous, on-demand regimen);
- sets of ***dosage*** (high dose, intermediate dose and low dose regimen);
- options in *care delivery* (home treatment/self administration, hospital or health station based,…).

Intervention 1.: What has the Global Initiative helped achieving so far?

Council of Europe/EDQM: "Guide to the preparation, use and quality assurance of blood components", Rec. No. 95(15) will have in its 19th edition a separate section on Cryoprecipitate-pathogen reduced (→Chapter 5 – Part D: Plasma Products); *N.B. Commission Directive 2016/1214 of 25 July 2016 amending Directive 2005/62/EC as regards QS Stds&Specs makes Guide legally binding, mandatory for EU MS*

International Society of Blood Transfusion (ISBT): intense work on "Cryo-VI" through its Working Party on Global Blood Safety (WP on GBS) →comprehensive set of recommendations on LP of Cryo-VI

WHO: treatment guidelines in Handbook of Appropriate Clinical Use of Blood (WHO/BTS/99.3, 2001) →revision process about to start; Expert Panel advocate for incorporation of Cryo-VI in revised clinical guide

N.B. WFH has also initiated the review process for their guidelines.

Global Initiative on "*LP of Cryo-VI in l-HDI*" (intervention 2.)

2. give high priority in relevant policies and strategies:

In developing countries, health care policies and strategies often follow after standards and guidelines have been set (S&G often taken up from outside).

Therefore, risks exist that policies do not reflect correctly national needs.

This applies to Cryo-VI, which is not even mentioned in existing S&G (this will change in the near future).

Policies, action plans, strategies need to be updated and should follow WHO formats (e.g. for national blood policies). They need to emphasize universal treatment principles, take into account existing diversities, consider the potential of novel technologies (e.g. VI on plasma and cryoprecipitate), take advantage of changing environment in the blood sector within health care systems and combine all elements into a comprehensive balanced approach addressing existing needs, problems and deficiencies in the different countries.

The Global Initiative is cooperating with WHO in moving forward this intervention, especially relating to national blood policies.

Global Initiative on "*LP of Cryo-VI in l-HDI*" (intervention 3.)

3. advocate and promote LP of Cryo-VI in l-HDI:

Efficient lobbying with stakeholders in a country is of paramount importance to introduce Cryo-VI (in a stepwise approach).

With governments or governmental agencies in developing countries, crucial issues need to be discussed and well argumented: safety, quality, supply, availability, accessibility, affordability and inhibitor problematic …and, last but not least, costs of all kinds (direct, indirect, hidden).

Ideally, WFH could support its NMO in l-HDI in their advocacy efforts.

National Hemophilia Associations (NHA) have high credibility to advocate for changes/improvements along the blood chain (production&usage).

WHO Country Offices in l-HDI as well as WHO Regional Offices will be able to exercise influence in promoting "LP of Cryo-VI", as they have experience and needed authority.

Global Initiative on "*LP of Cryo-VI in l-HDI*" (intervention 4.)

4. run a pilot project:

The purpose of the PP is to field test in l-HDI existing technologies for viral inactivation of cryoprecipitate.

It is designed as a feasibility study on implementing (and maintaining) SD/F production for cryoprecipitate in developing countries, based on selected pilot sites being largely representative for situations in l-HDI.

Premises, equipment and staff are in place in selected blood centers (BC);

budgets for PP are needed to support pilot sites with:

- training&education (BC staff; also clinicians in using local products);
- quality management and work flows (if adjustments are necessary);
- personnel (additional, if needed);
- material (kits for Cryo-SD/F® to locally produce Cryo-VI).

Intervention 4.: What has the Global Initiative achieved so far?

- ✓ Concept elaborated for PP
- ✓ Pilot sites recruited
- ✓ Logical framework agreed with the pilot sites
- ✓ Several assessments in blood centers conducted
- ✓ Necessary funds secured (ALH, private sponsors, banks,…)
- ✓ Regulatory affairs being dealt with in index countries
- ✓ Medical devices for Cryo-SD/F® ordered from VIPS

N.B.

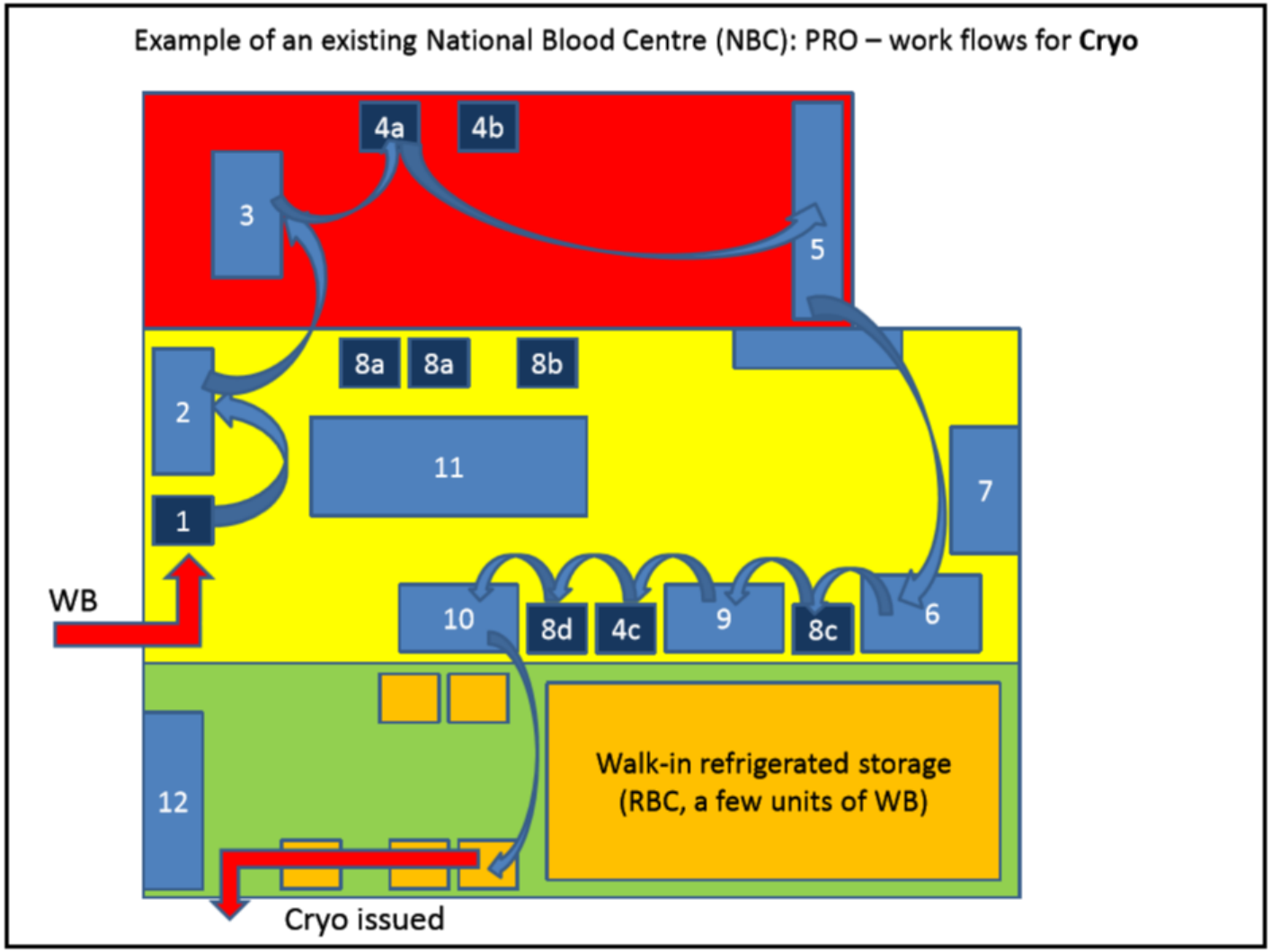
On January 31, 2017, ALH has applied for a research grant with WFH (amounting 50 000 USD)… ALH is still hoping to gain WFH support.

Logical Framework of the Pilot Project for pilot sites

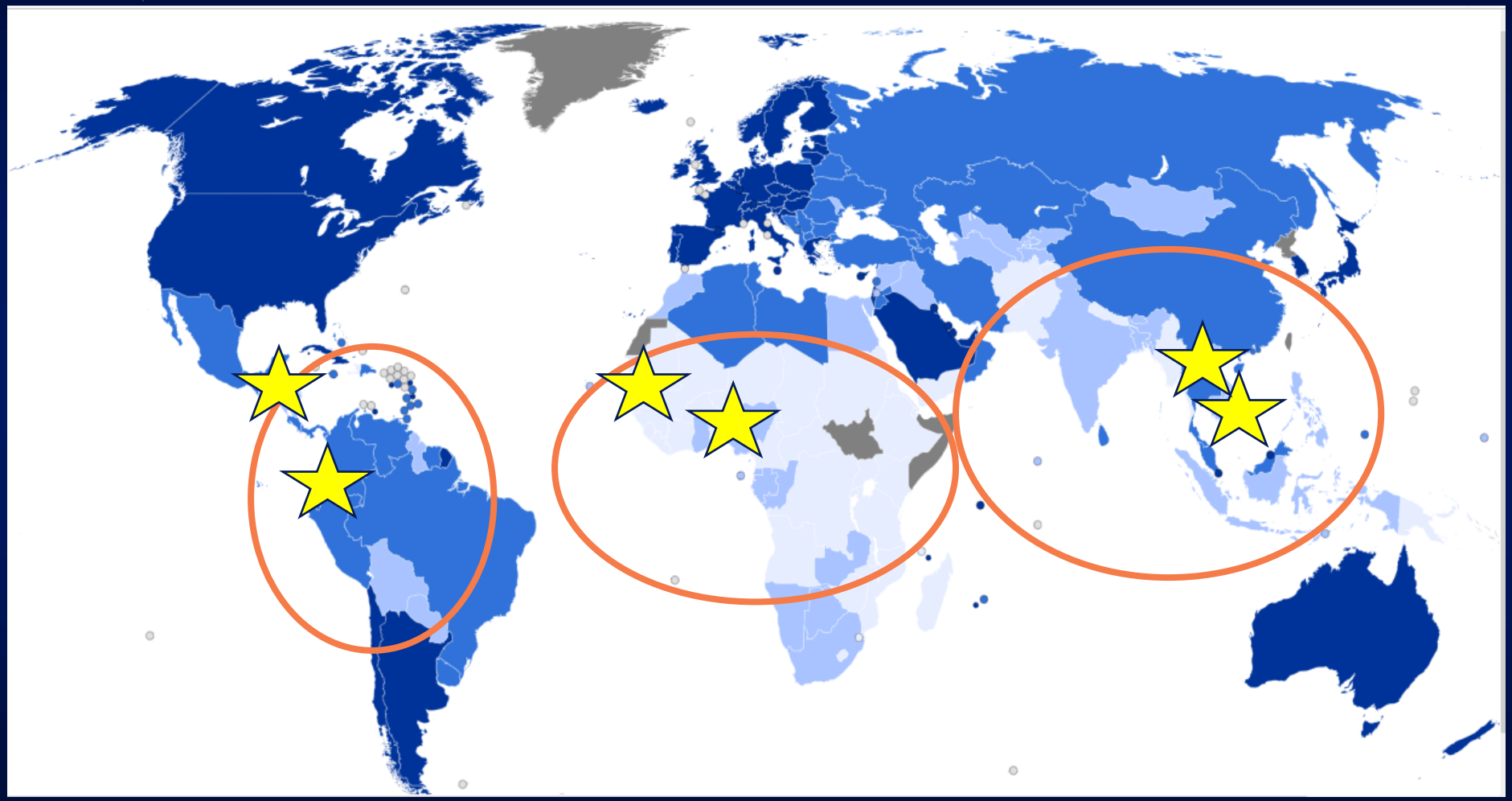
Local Preparation of Cryoprecipitate-Pathogen Reduced in selected blood centres in developing countries» (LP of Cryo-PR in LDIs)

INTERVENTION LOGIC	OBJECTIVELY VERIFIABLE INDICATORS (OVI)	MEANS AND SOURCES OF VERIFICATION (MSV)	HYPOTHESES (H), PREREQUISITE CONDITIONS (CP) AND RISKS (R)
GLOBAL OBJECTIVE			
Contribute to improvement of medical treatment of patients with bleeding disorders, especially in developing countries			
SPECIFIC OBJECTIVE			**Contributing to the global objective**
Facilitate introducing, implementing and maintaining local preparation of hemostatic products for the treatment of patients with bleeding disorders in selected blood centres in the developing world, especially the local preparation (LP) of cryoprecipitate-pathogen reduced (Cryo-PR)	- Quality: all selected blood centres are in compliance with Good Manufacturing Practices (GMP) - Safety: all selected blood centres produce all cryoprecipitates using a validated pathogen reduction technique before release - Supply and Availability: all	- Quality: Audits conducted by teams set up by WFH in collaboration with partners - Safety: Monthly statistics by selected blood centres and periodic reports by WFH - Supply and Availability: Monthly statistics by selected blood centres and periodic reports by WFH	- Commitment of the Health Authorities responsible for the selected blood centres to support local preparation of products for patients with bleeding disorders (Cryo-PR) (CP) - National Blood Policy updated for LP of Cryo-PR (CP) - Regulatory Agency to authorize use of technologies for Cryo-PR (CP)

Assessment of several pilot sites, checking compliance with GP



PP on LP of Cryo-VI in l-HDI



Developing countries → low HDI (l-HDI) with score < 0,600

Global Initiative on "*LP of Cryo-VI in l-HDI*"

For 5. "establish an expansion programme for *LP of Cryo-VI in l-HDI"* and 6. "contribute to activities for sustainability": plans exist, they need to be adapted according to lessons from PP.

In addition, flanking activities to support the 6 "core" interventions:

- **Twinning** programmes between blood centers
  (→ *in cooperation with Blood Services in developed countries*)
- **Research** on new technologies for Local Cryo-VI
  (→ *in cooperation with ISBT and industry*)
- **Training** Programmes
  (→ *using WHO's worldwide Network of Collaborating Centers*)
- **Lobbying** programmes
  (→ *with NHA, ?WFH assisting their NMOs in l-HDI*),…
- **IEQAS** for therapeutic products
  (→ *WHO's Network of Collaborating Centers and twinned BCs*), …

Role of National Hemophilia Associations (NHA)

NHA in l-HDI have to play an important role in influencing both arms of the blood system: **production and usage** of blood products.

They should advocate for:

1. building on existing national blood systems (and integrating local preparation of Cryo-VI)
2. improving blood policies and extending coverage to Cryo-VI;
3. incorporating additional safe blood products into national blood programmes;
4. facilitating local preparation of hemostatic products, safeguarded by VI-technologies, through reviewed national blood plans, quality manuals, standards&guidelines,…

NHA should also promote the usage of local Cryo-VI with patients, prescribing physicians, hospitals, blood banks,…

Global Initiative on "*LP of Cryo-VI in l-HDI*"… **extended**

The Global Initiative on "Local Cryo-VI in l-HDI" was started to help PWH in resource limited countries, it was triggered by unchanged catastrophic supplies.

With time, another serious problem has been taken up by the Global Initiative: inhibitors induced by substitution therapy (also, unchanged for many years).

Once Cryo-SD/F becomes available in l-HDI, the Global Initiative proposes to conduct **INH studies** with severe hemophilia A PUPs:

- treat initially with Cryo-VI for 10-20 injection days,
- check for the presence of INH,
- change to CFC (if available; if not, continue with local Cryo-VI).

SIPPET= Survey of Inhibitors in Plasma-Product Exposed Toddlers
France-Coag =Analysis of data from the FranceCoag cohort

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A

F. Peyvandi, P.M. Mannucci, I. Garagiola, A. El-Beshlawy, M. Elalfy, V. Ramanan, P. Eshghi, S. Hanagavadi, R. Varadarajan, M. Karimi, M.V. Manglani, C. Ross, G. Young, T. Seth, S. Apte, D.M. Nayak, E. Santagostino, M.E. Mancuso, A.C. Sandoval Gonzalez, J.N. Mahlangu, S. Bonanad Boix, M. Cerqueira, N.P. Ewing, C. Male, T. Owaidah, V. Soto Arellano, N.L. Kobrinsky, S. Majumdar, R. Perez Garrido, A. Sachdeva, M. Simpson, M. Thomas, E. Zanon, B. Antmen, K. Kavakli, M.J. Manco-Johnson, M. Martinez, E. Marzouka, M.G. Mazzucconi, D. Neme, A. Palomo Bravo, R. Paredes Aguilera, A. Prezotti, K. Schmitt, B.M. Wicklund, B. Zulfikar, and F.R. Rosendaal

ABSTRACT

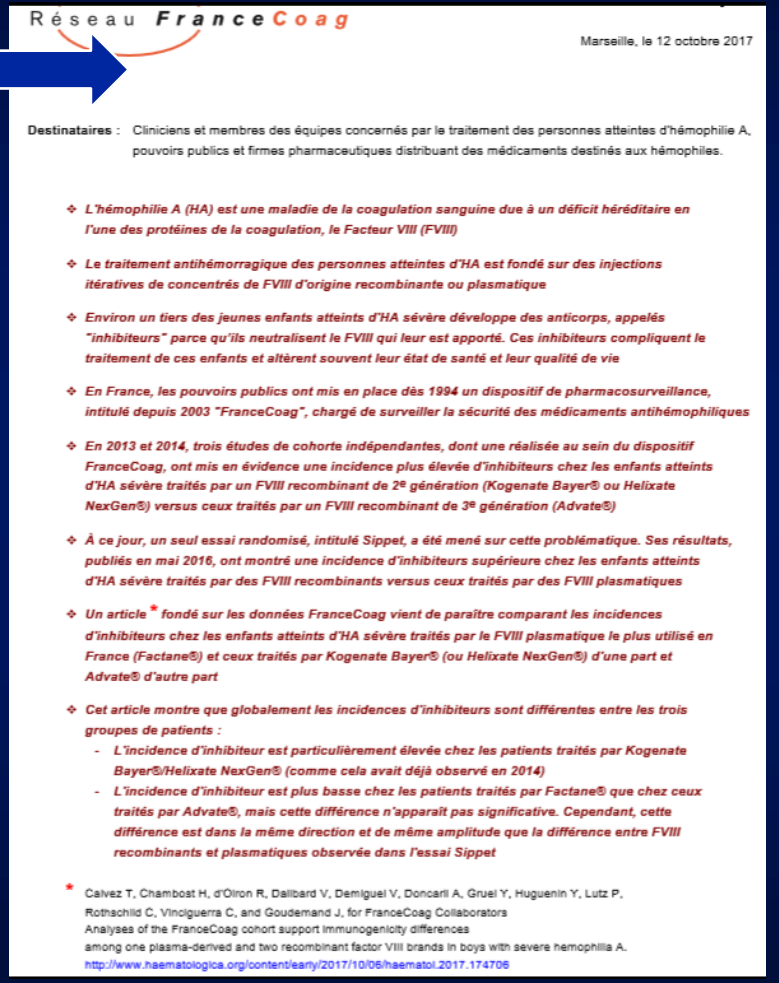
BACKGROUND

The development of neutralizing anti–factor VIII alloantibodies (inhibitors) in patients with severe hemophilia A may depend on the concentrate used for replacement therapy.

METHODS

We conducted a randomized trial to assess the incidence of factor VIII inhibitors among patients treated with plasma-derived factor VIII containing von Willebrand factor or recombinant factor VIII [illegible]nts who met the eligibility criteria (male sex, age <6 years, severe hemophili[illegible]previous treatment with any factor VIII concentrate or only minimal treat[illegible]u blood components) were included from 42 sites.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Peyvandi at the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, and Department of Pathophysiology and Transplantation, University of Milan, Via Pace 9, 20122 Milan, Italy, or at flora.peyvandi@unimi.it.



Réseau FranceCoag

Marseille, le 12 octobre 2017

Destinataires : Cliniciens et membres des équipes concernés par le traitement des personnes atteintes d'hémophilie A, pouvoirs publics et firmes pharmaceutiques distribuant des médicaments destinés aux hémophiles.

- *L'hémophilie A (HA) est une maladie de la coagulation sanguine due à un déficit héréditaire en l'une des protéines de la coagulation, le Facteur VIII (FVIII)*
- *Le traitement antihémorragique des personnes atteintes d'HA est fondé sur des injections itératives de concentrés de FVIII d'origine recombinante ou plasmatique*
- *Environ un tiers des jeunes enfants atteints d'HA sévère développe des anticorps, appelés "inhibiteurs" parce qu'ils neutralisent le FVIII qui leur est apporté. Ces inhibiteurs compliquent le traitement de ces enfants et altèrent souvent leur état de santé et leur qualité de vie*
- *En France, les pouvoirs publics ont mis en place dès 1994 un dispositif de pharmacosurveillance, intitulé depuis 2003 "FranceCoag", chargé de surveiller la sécurité des médicaments antihémophiliques*
- *En 2013 et 2014, trois études de cohorte indépendantes, dont une réalisée au sein du dispositif FranceCoag, ont mis en évidence une incidence plus élevée d'inhibiteurs chez les enfants atteints d'HA sévère traités par un FVIII recombinant de 2e génération (Kogenate Bayer® ou Helixate NexGen®) versus ceux traités par un FVIII recombinant de 3e génération (Advate®)*
- *À ce jour, un seul essai randomisé, intitulé Sippet, a été mené sur cette problématique. Ses résultats, publiés en mai 2016, ont montré une incidence d'inhibiteurs supérieure chez les enfants atteints d'HA sévère traités par des FVIII recombinants versus ceux traités par des FVIII plasmatiques*
- *Un article * fondé sur les données FranceCoag vient de paraître comparant les incidences d'inhibiteurs chez les enfants atteints d'HA sévère traités par le FVIII plasmatique le plus utilisé en France (Factane®) et ceux traités par Kogenate Bayer® (ou Helixate NexGen®) d'une part et Advate® d'autre part*
- *Cet article montre que globalement les incidences d'inhibiteurs sont différentes entre les trois groupes de patients :*
  - *L'incidence d'inhibiteur est particulièrement élevée chez les patients traités par Kogenate Bayer®/Helixate NexGen® (comme cela avait déjà observé en 2014)*
  - *L'incidence d'inhibiteur est plus basse chez les patients traités par Factane® que chez ceux traités par Advate®, mais cette différence n'apparaît pas significative. Cependant, cette différence est dans la même direction et de même amplitude que la différence entre FVIII recombinants et plasmatiques observée dans l'essai Sippet*

* Calvez T, Chambost H, d'Oiron R, Dalibard V, Demiguel V, Doncarli A, Gruel Y, Huguenin Y, Lutz P, Rothschild C, Vinciguerra C, and Goudemand J, for FranceCoag Collaborators
Analyses of the FranceCoag cohort support immunogenicity differences among one plasma-derived and two recombinant factor VIII brands in boys with severe hemophilia A.
http://www.haematologica.org/content/early/2017/10/06/haematol.2017.174706

EMA (15.09.2017):
« *…no clear and consistent evidence* of a difference in the risk of inhibitor development r-CFC and pd-CFC… »
What about the *very high incidence of INH?*
What about the ***precautionary principle***?

Global Initiative on "*LP of Cryo-VI in l-HDI*"… **extended**

F.VIII products come with a serious problem: **inhibitor** formation (INH).

Clotting factor concentrates (CFC, purchased or donated) should not bring "more bad than good" to developing countries:

1. 25-35% of Hem.A PUP develop an INH with F.VIII CFC (*SIPPET NEJM, 2016*); many believe that recombinant CFC are more likely to trigger an INH than plasma-derived
2. the majority of products donated now by industry are recombinant CFC
3. the incidence of INH induced by r-CFC is possibly as high as 50% (1 in 2), if patients are treated for the 1st time, while being in "immunological storm" (trauma, emergencies, massive bleeds) and if they are from Black populations
4. patients in l-HDI forming an INH are very likely "lost".

Cryoprecipitate has a low incidence of inhibitors (some 5%).

Final considerations

- The existing situation in treatment of patients with bleeding disorders in developing countries must change.
- Recent developments open a new treatment option with Cryo-VI, if CFC are not available: 1. improvement in the blood sector in most developing countries, 2. availability of VI-technologies (f.ex. to make Cryo-SD/F).
- A worldwide initiative can bring “Local Cryo-VI” into developing countries, involving WHO, ISBT, NHA and others (?WFH).
- If implemented at a larger scale in l-HDI, ***local preparation of Cryo-VI*** can significantly improve quality&safety of hemostatic products and manage threats resulting from supply, availability, accessibility& affordability, but also from inhibitors.
- Cryo-VI will benefit ***patients with hemophilia A, Willebrand disease and fibrinogen deficiency in developing countries, but also women with fibrinogen depletion at child delivery, lowering also maternal mortality.***

Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2013), **19**, 1 DOI: 10.1111/hae.12074

COMMENTARY

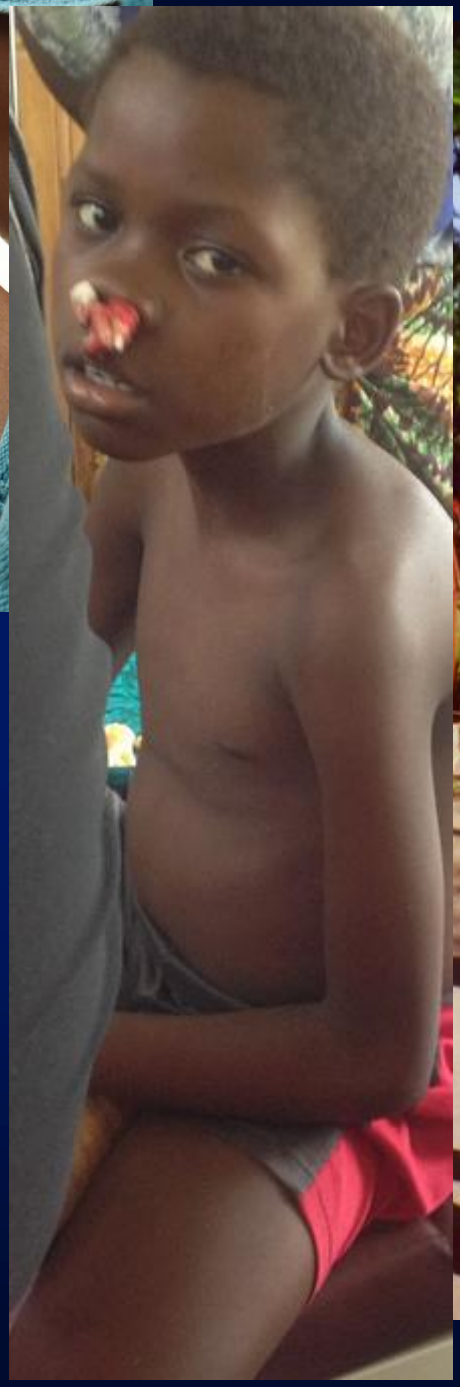
The World Federation of Hemophilia guideline on management of haemophilia

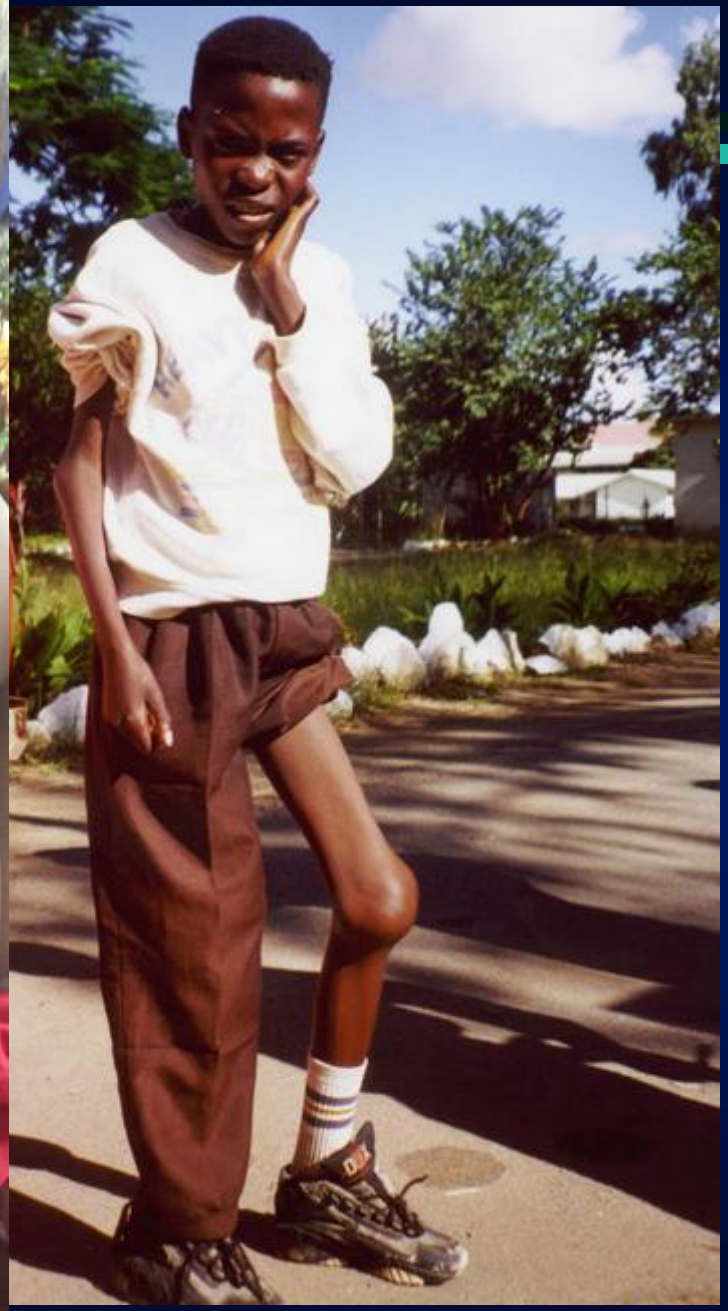
M. MAKRIS*† and C. KASPER‡

**Department of Cardiovascular Science, University of Sheffield, Sheffield; †Sheffield Haemophilia and Thrombosis Centre, Royal Hallamshire Hospital, Sheffield, UK; and ‡Los Angeles Orthopaedic Hospital and Keck School of Medicine, University of Southern California, Los Angeles, CA, USA*

Established 50 years ago in 1963, the World Federation of Hemophilia (WFH) is the international organization representing the inherited bleeding disorder community. One of its functions is to produce literature that can be used internationally in countries irrespective of wealth (and thus availability of clotting factor concentrate) or language. The premier guideline produced by the organization is one of primary, secondary and tertiary prophylaxis included in this guideline, were only approved by the FVIII and IX subcommittee of the International Society on Thrombosis and Haemostasis at their Liverpool meeting in June 2012. The whole manuscript is very well referenced and most of the key papers in haemophilia management are included.

"… we must never lose sight of the fact that many patients in the world have little or no access to any clotting factor treatment and the *WFH continues to work to achieve sustainable comprehensive care and treatment for all.*"





They thank you very much !