

# Recombinant or plasma-derived products for haemophilia? *a personal view*

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ORIGINAL ARTICLE

# Haemophilia care in Europe: a survey of 19 countries

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**Summary.** In 2009, a questionnaire was circulated to 19 national haemophilia patient organizations in Europe affiliated to the European Haemophilia Consortium (EHC) and the World Federation of Hemophilia (WFH) to seek information about the organization of haemophilia care and treatment available at a national level. The responses received highlighted differences in the level of care despite the recent promulgation of consensus guidelines designed to standardize the care of

haemophilia throughout the continent of Europe. There was a wide range in factor VIII consumption with usage ranging from 0.38 IU per capita in Romania to 8.7 IU per capita in Sweden (median: 3.6 IU per capita). Despite the specific inclusion of coagulation factor concentrate in the WHO list of essential medications, cryoprecipitate is still used in some eastern European countries.

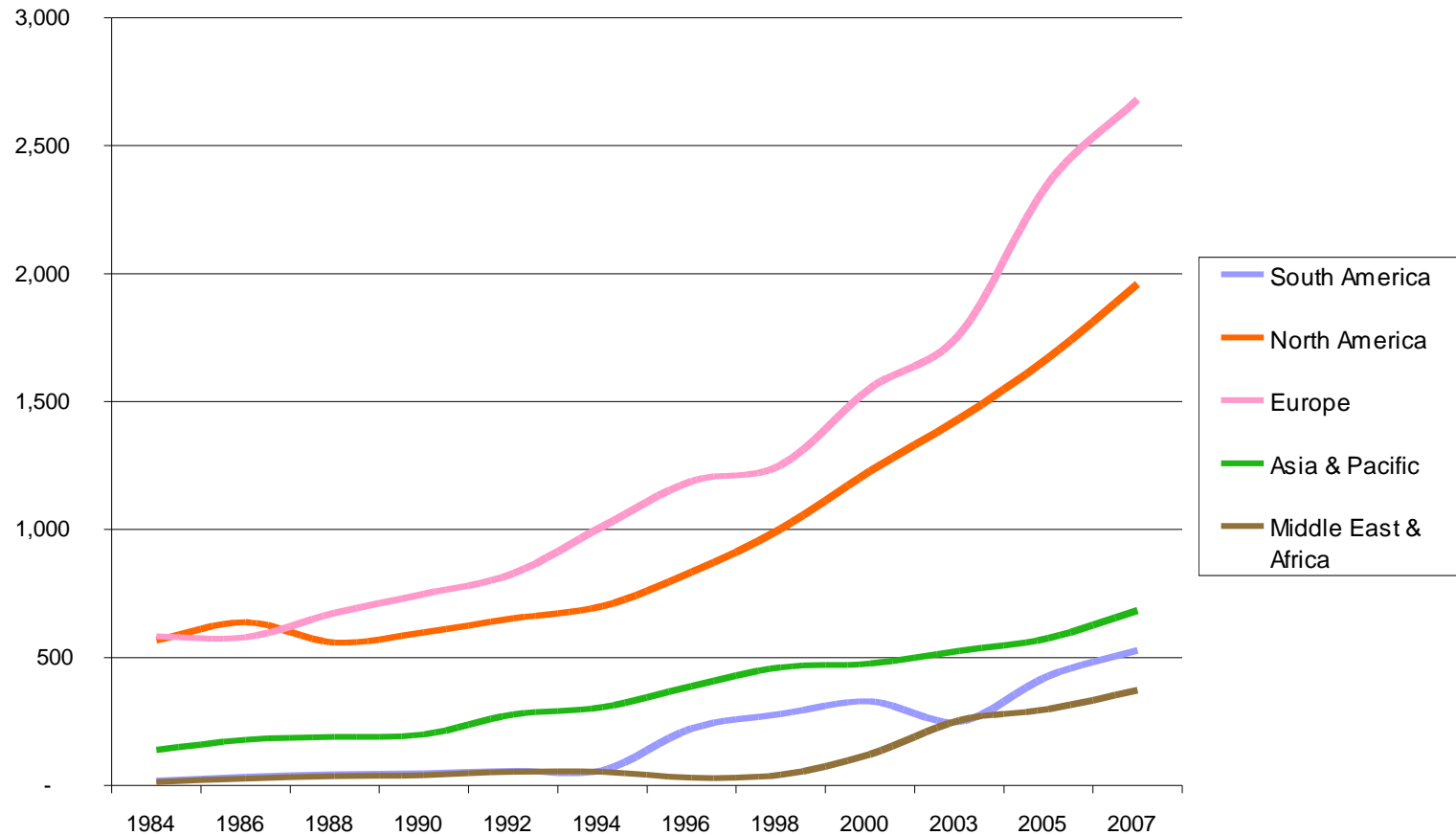
**Keywords:** organisation, treatment, specialist care

# Recombinant or plasma derived?

- There is a still need for both types of product and will be for many years to come
- The cost differential has been significantly eroded:
  - recombinant FVIII now cheaper than plasma products in the UK
- Pathogen safety remains the main advantage of recombinant products
- No proven increase in risk of inhibitor development
- The development of new products is wholly based on recombinant technology
- Patient choice should be respected

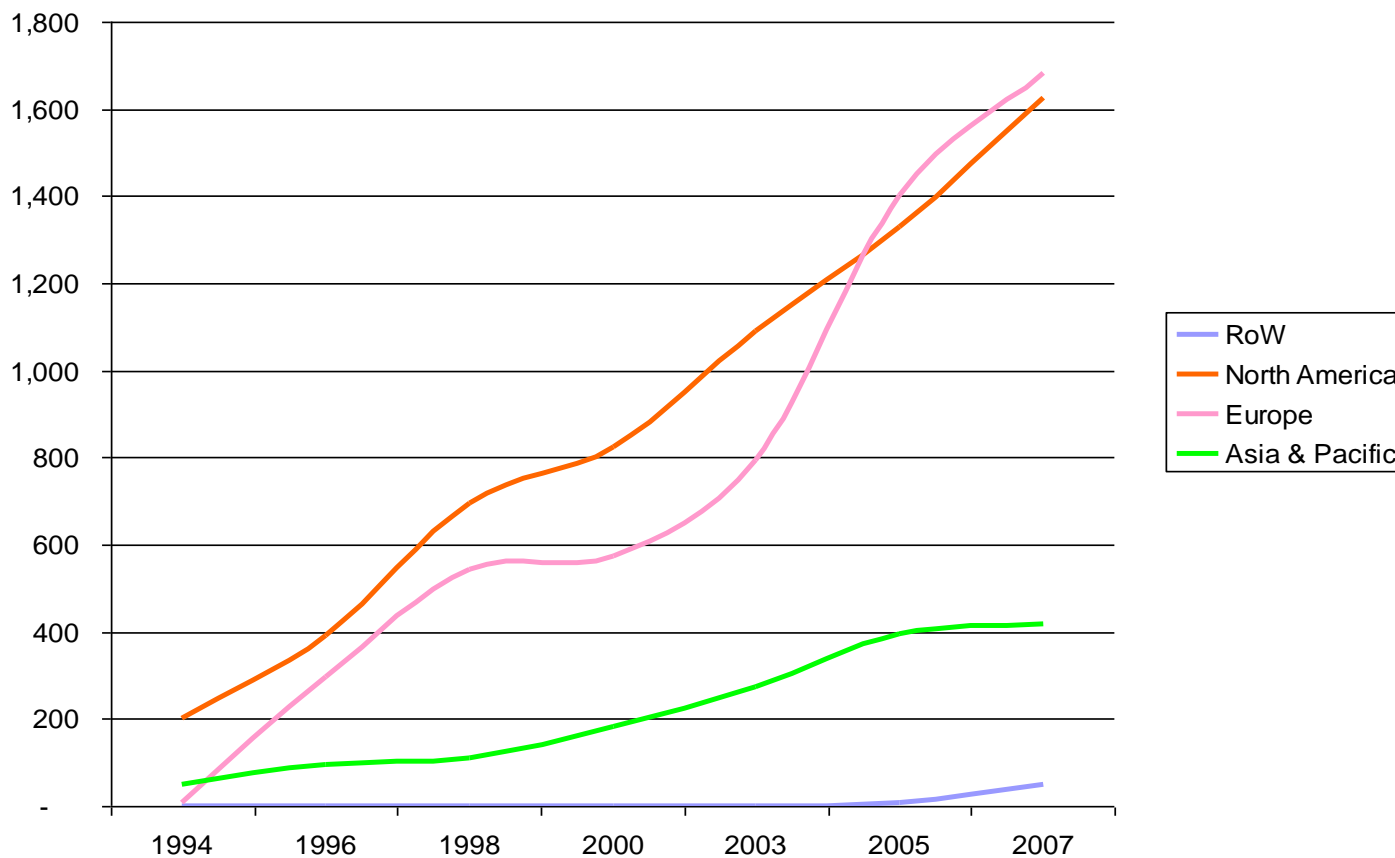
# TRENDS IN COAGULATION FACTORS SUPPLY AND DEMAND

GLOBAL FACTOR VIII CONSUMPTION BY REGION FROM 1984 TO 2007  
PLASMA-DERIVED AND RECOMBINANT  
(International Units x 1,000)



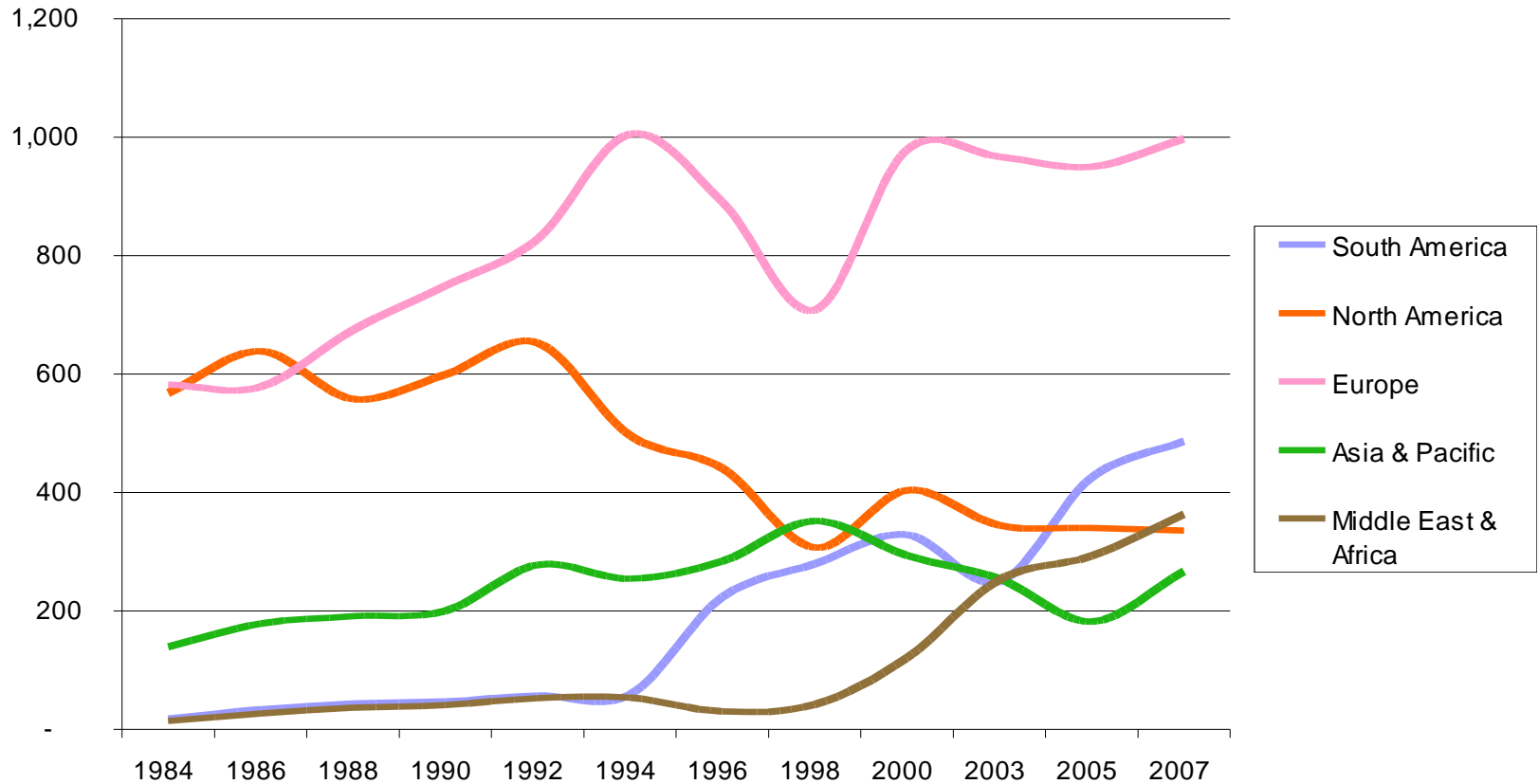
# TRENDS IN COAGULATION FACTORS SUPPLY AND DEMAND

GLOBAL FACTOR VIII CONSUMPTION BY REGION FROM 1984 TO 2007  
RECOMBINANT  
(International Units x 1,000)



# TRENDS IN COAGULATION FACTORS SUPPLY AND DEMAND

GLOBAL FACTOR VIII CONSUMPTION BY REGION FROM 1984 TO 2007  
PLASMA-DERIVED  
(International Units x 1,000)



# Cost of coagulation factor concentrates:

- Price of products has fallen significantly recently:
  - Price of recombinant FVIII in UK now lower than many plasma-derived products following national tender
- Other companies now developing recombinant factor VIII and IX preparations:
  - Greater competition will reduce prices further
- Buying concentrate can prove cheaper than building own national fractionation plant or contract fractionation
  - Costs of production of cryoprecipitate often underestimated



# FIGHT THE BITE!

## JOIN THE "SWAT TEAM" AGAINST WEST NILE VIRUS

West Nile Virus is a common mosquito-borne virus that can cause illness in humans. It is spread by mosquitoes that bite humans and animals. The virus is most common in the summer and fall months. Symptoms include fever, headache, and muscle pain. In some cases, it can lead to more serious complications like encephalitis or meningitis.

Prevention tips: Use mosquito repellent, wear long sleeves and pants, and eliminate standing water around your home.

### Protect yourself against AVIAN & HUMAN FLU

Coughs, colds, sore throats and runny noses are common and usually no cause for alarm. However, a new strain of influenza has emerged in birds that in very rare cases can affect humans. If it's not properly controlled there are concerns that one day it will be able to spread more easily among humans.

The best way to protect your family is to start now.

Simple steps include:

- Avoid all unnecessary contact with both live and dead birds
- Report suspect bird cases to the relevant authorities
- Take special precautions when preparing and cooking poultry

And most IMPORTANT of all!

- Improve personal hygiene (including covering coughs and sneezers and frequent hand-washing)

This leaflet explains how.

### Avian Influenza

Avian Influenza or "bird flu" is a highly contagious disease that affects poultry. Once infected, both domestic and wild birds (including chickens, ducks, geese and turkeys) can become sick and die. Scientists call the virus "H5N1".

The virus spreads easily from bird to bird through infected droplets. Migratory birds can spread the disease great distances. The only way to control the spread of disease is to cull the birds on infected farms. This sounds harsh but the disease is so contagious it will quickly spread to other areas.

# PLAGUE FROM THE SKIES

## A terrifying virus carried by birds has arrived in Britain

## Mortality before and after HIV infection in the complete UK population of haemophiliacs

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 on behalf of the UK Haemophilia Centre Directors' Organisation‡

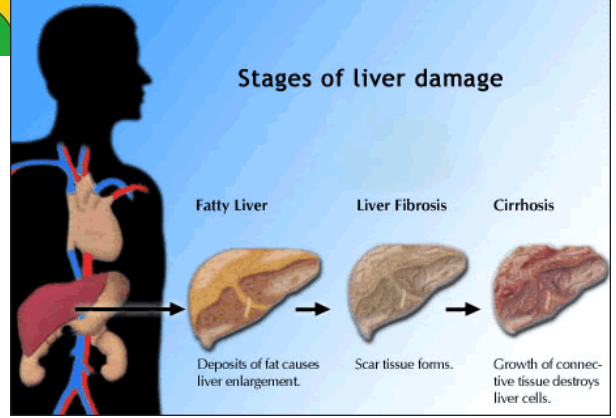
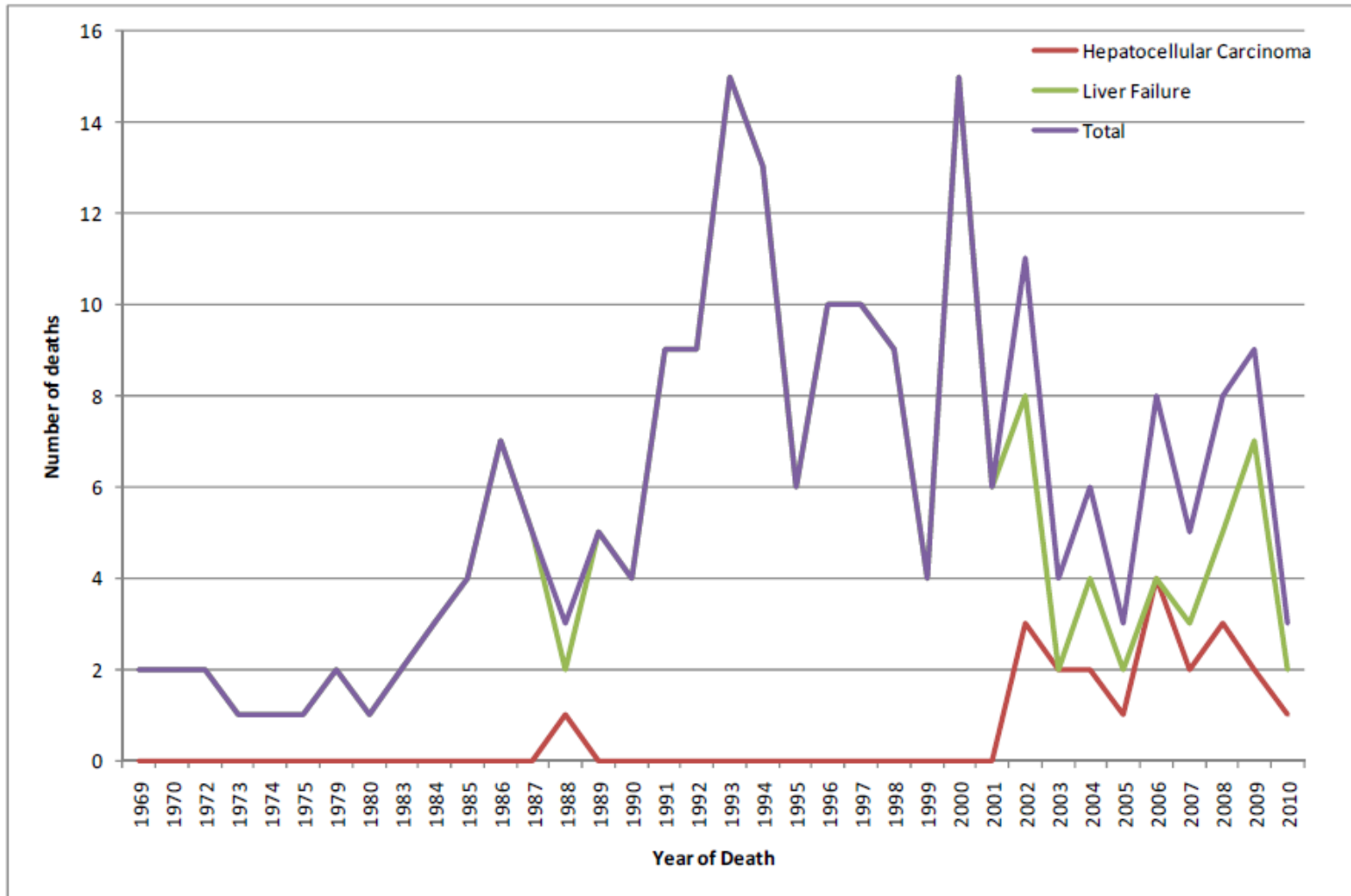


Figure 18 - Annualised UK Deaths from Liver Disease 1969-2010



# Focus on safety has enhanced virus removal and pathogen inactivation

Virus removal	Pathogen inactivation
<ul style="list-style-type: none"><li>• Plasma fractionation</li><li>• Filtration methods</li><li>• Various chromatographic methods</li></ul>	<ul style="list-style-type: none"><li>• Pasteurization</li><li>• Solvent/detergent (S/D) treatment</li><li>• High salt, alcohol or acid treatment</li><li>• Vapour heat treatment</li></ul>

1. Most plasma products now subject to two methods of viral elimination
2. These methods also kill newer viruses (SARS, avian influenza, West Nile virus)
3. Not all pathogens are inactivated by these methods e.g parvovirus B19 and prions

## Race to find patients at risk of CJD

By David Charter  
Health Correspondent

THE Government was wrong last night to ease some of the restrictions at risk from catching the human form of "mad cow" disease after admitting that 1915 patients were treated with blood products from a man who died of vCJD.

Ministers immediately announced revised criteria for patients and their families who will face an agonising wait to learn if they carried the disease.

The admission last night by Lord Hunt of Kings Heath, the junior Health Minister, will alarm Britain's 8,000 haemophiliacs. The discipline dates to the 1970s blood conservation scandals when 4,000 haemophiliacs contracted hepatitis C and 1,200 caught HIV.

The disclosure came as one of the Government's advisers on vCJD accused ministers of "seriously misleading" the public over the safety of hospital treatments. Michael Bangor, the chairman of a group of experts set up to control vCJD, criticised getting the CJD boardroom "out over his concerns about surgery."

In a letter to Lord Donaldson, the Chief Medical Officer, he accused the Government of not taking the panel seriously. Civil Service support of the panel was a "hoax" too, he said. He did not know from one day to the next which off-

Professor Donaldson's desk at Parliament heard that scientists were checking hospital records at 100 hospitals every haemophiliac were given a clotting agent made from a blood donor in 1976 to 1987 who later it turned out had vCJD.

The Government limited the use of British plasma in the manufacture of blood products in 1998 as a precautionary measure against the risk that vCJD can be transmitted by this way. Lord Morris of Manchester, the Labour peer who is honorary president of the Haemophilia Society, said: "This has come as a devastating shock to the haemophiliac community who have already been struck by HIV and hepatitis C infection in the case of 5015 treatment."

He added: "I will be discussing the minister's reply very vigorously with the Haemophilia Society. No one seems to know how many people may be affected but the society is doing all it can to ensure families that have cause to believe they were affected. The implications are very serious."

Lord Hunt admitted that it was not sure if all haemophiliacs might have been affected but sought to play down the risks. He said: "We would stress that any risk of transmission of vCJD through blood products is theoretical. There have been no reported cases of vCJD among the haemophiliac community."

It remains to be seen, using the incubation period now too long to be at all certain.

It took issue with a statement from John Denham, the Health Minister, who said: "We have no evidence of any patient being infected with variant CJD in hospital, but while we are still learning about the progress of vCJD we should take precautions to reduce the theoretical risk of transmission."

Professor Hawry said that "simply overstated" the fact that the vCJD incubation period could be 20 years and was therefore "not as reassuring as it may seem."

Earlier this month ministers announced £20 million to improve hospital ventilation, including £25 million for disposable instruments for all hospital activities. Professor Hawry argued that all high-risk operations should be performed with disposable instruments.

He said: "While we're with it, the Department of Health would intend to reassure the public, it is a matter of great concern if the public is misled, even as a result of lack of care in writing up the current state of knowledge to a clear and frank form."

In the letter he added: "The course of events up to this point may suggest to the public that the Department of Health is not taking seriously the very important issues of public health which are the



## Briton takes lead in solo yacht race

By Edward Gorman  
Sailing Correspondent

THE British yachtsman Iain MacArthur took another step towards the greatest prize in single-handed sailing yesterday when he took the lead in the Volvo Ocean Race, having today taken the world lead for the first time.

On the third day ahead of his 16th yacht, *Kingsaker*, the 24-year-old from Whitby had sailed with an 11-hour margin to the French single-handed sailor Michel Desjoyeaux in the two skippers' locked the race into a tight race, just north of the Cape of Good Hope.

With only 3,000 miles of the 24,000-mile race left to sail, it is neck-and-neck between the young English seaman, who is already a two-fold hero in France, and Desjoyeaux, an acknowledged master of single-handed sailing known in France as "le professeur".

Michelle French, the Volvo Ocean Race Director, was the first to tell MacArthur that she was ahead when he contacted her on the radio yesterday. "I'm happier but I don't share my happiness when I'm seen to be victorious," she said. "I think Michel is better positioned to escape this in the northwest and the weather for the other sailors coming from behind."

The next two weeks have seen MacArthur "completely make up his mind on Desjoyeaux". When the Frenchman rounded Cape Horn he had a lead of more than 100 miles and some believed the race was all but over. However, MacArthur fought back every inch of the way as the two headed north up the East American coast.

# vCJD and haemophilia in the UK:

Zaman SM et al. Haemophilia 2011

- BSE first identified in UK cattle in 1985
- vCJD recognised as human equivalent of BSE in 1996
- UK acknowledged as epicentre of infection
- Asymptomatic prion carriers identified in histological study of general population in UK
- vCJD can be transmitted by whole blood
- 787 patients with haemophilia received “implicated batches” between 1987-1999
- No patient with haemophilia has developed vCJD but recent case report of prions in spleen *post mortem*

*Peden A et al. Haemophilia 16: 296-304 (2010):*

GUIDELINES

Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders

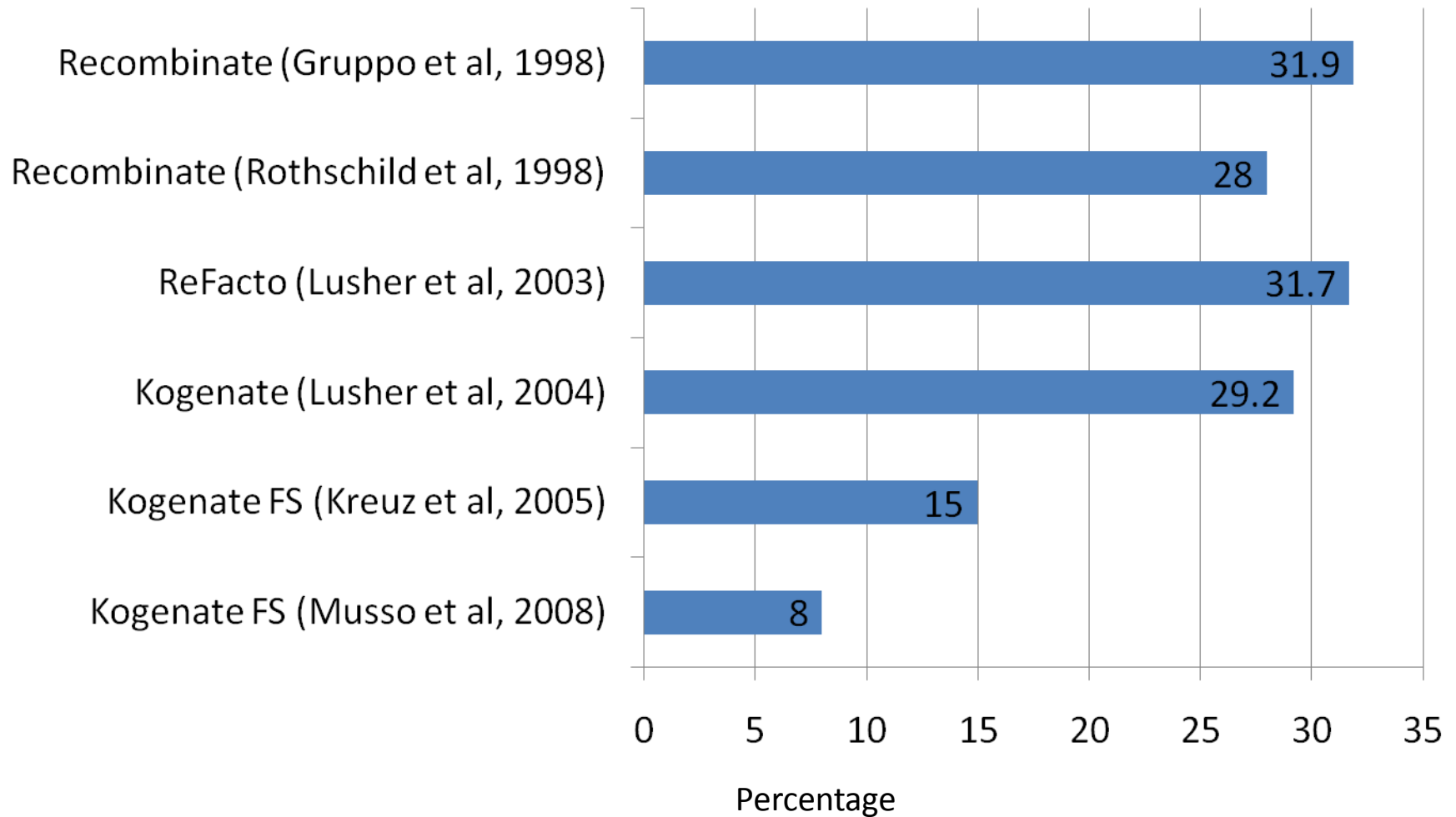
UNITED KINGDOM HAEMOPHILIA CENTRE DIRECTORS ORGANISATION EXECUTIVE COMMITTEE

“Recombinant factor VIII is the treatment of choice for all patients.”

UKHCDO: 1997

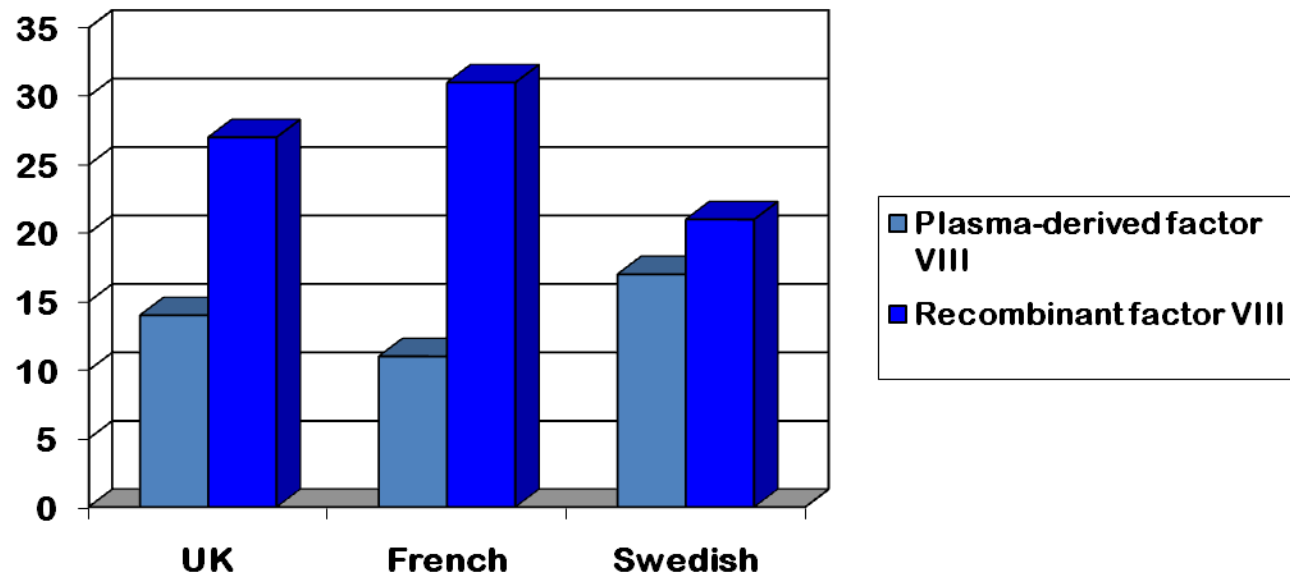
Haemophilia 3: 63-77

# Inhibitor incidence in PUPs with severe hemophilia A



# PUP studies suggest that risk for inhibitors is lower with plasma-derived FVIII

- Three comparative historical cohort studies
- Difference was only statistically significant in two studies



# Factors to consider when evaluating studies of inhibitor incidence

## Trial design

- Is the trial prospective or retrospective?
- Is the trial looking at incidence or prevalence?

## Inhibitor assay and frequency of testing

- Was the trial conducted prior to the mid-1990s without the Nijmegen modification?
- What was the frequency of testing for inhibitors?
- Low titre versus high titre, transient versus persistent

## Patient population characteristics

- Does the trial report separate incidence in PUPs/MTPs from that in PTPs?
- Does the trial report details of patients at higher risk for inhibitor development?

# Factors to consider when evaluating studies of inhibitor incidence: trial design

Is the trial prospective or retrospective?

- Analysis of **retrospective** trials of plasma-derived concentrates indicated an overall average incidence of inhibitor of approximately 11% (Gringeri et al, 2006)
- A **prospective** study of plasma-derived concentrates found that inhibitors developed in 24% (15/63) of all haemophilia A patients, and in 52% (14/27) of those with severe disease (Ehrenforth et al, 1992)

Is the trial looking at incidence or prevalence?

- Incidence estimates the number of new cases of inhibitors during a given time period
- Prevalence estimates the total number of cases of inhibitors in a given population at a given time
- Many early plasma-derived FVIII product trials reported inhibitor prevalence, thereby underreporting transient inhibitors and those eradicated by ITI

**Table 9 - Inhibitors by disease severity**

Diagnosis	Number of Patients ever known to have an inhibitor by disease severity								
	≤ 1 iu/dl			>1 and <5 iu/dl			≥ 5 iu/dl		
	In Reg	Inhib. Pts	%	In Reg	Inhib. Pts	%	In Reg	Inhib. Pts	%
Haemophilia A	1814	351	19.35%	559	43	7.69%	2972	62	2.09%
Haemophilia B	396	15	3.79%	244	0	0.00%	482	0	0.00%
von Willebrand disease	125	2	1.60%	164	2	1.22%	8381	6	0.07%

Diagnosis	Patients with a current inhibitor treated between April 2009 and March 2010 by disease severity								
	≤ 1 iu/dl			>1 and <5 iu/dl			≥ 5 iu/dl		
	In Reg	Inhib. Pts	%	In Reg	Inhib. Pts	%	In Reg	Inhib. Pts	%
Haemophilia A	1655	146	8.82%	358	13	3.63%	848	20	2.36%
Haemophilia B	335	10	2.99%	134	0	0.00%	147	0	0.00%
von Willebrand disease	47	2	4.26%	50	1	2.00%	862	4	0.46%

# Factors to consider when evaluating studies of inhibitor incidence: inhibitor testing

Was the trial conducted prior to the mid-1990s without the Nijmegen modification?

- The Nijmegen modification to the Bethesda assay was adopted in the mid-1990s and improved accuracy
- Most plasma-derived FVIII trials were conducted prior to this
- As a consequence, they are likely to underreport inhibitors

What was the frequency of testing for inhibitors?

- Prospective trials for recombinant factor VIII products test for inhibitor formation after few exposures to FVIII
- Older trials of plasma-derived FVIII products only tested for inhibitors annually or when a patient demonstrated reduced recovery, thus underreporting incidence

Low titer versus high titer, transient versus persistent

- The characteristics, and clinical importance, of an inhibitor can change over time

# Factors to consider when evaluating studies of inhibitor incidence: the patient population

Does the trial report separate incidence in PUPs/MTPs from that in PTPs?

- Most inhibitors develop early during a patient's exposure to FVIII (within the first 50 exposure days)
- Ideally, trials should separate incidence in previously untreated and minimally treated patients from that in previously treated patients

Does the trial report details of patients at higher risk for inhibitor development?

- Patients of African or Latino descent, those with severe haemophilia A or a family history of inhibitors and large mutations are at higher risk for inhibitors
- Many older plasma-derived FVIII trials provide no detail on patient characteristics, making direct comparison between trials difficult

# The Canadian experience:

*Giles AR et al. Transfusion Science 19: 139-148 (1998)*

- Canada was the first country to switch to recombinant factor VIII for all (1994).
- 478 patients (PTPs) followed up for one year after switching to Kogenate
- Central laboratory used to screen patients before and 6 and 12 months after switch
- “The use of recombinant FVIII in hemophiliacs previously treated with plasma derived products was not associated with an increase in FVIII inhibitor development.”

# UK study of risk factors:

Maclean PS et al. Haemophilia (2010)

- National retrospective case control study
- 78 inhibitor patient identified over 25 year period (1982-2007)
- Age matched control selected for each case
- Data on potential genetic and treatment related risk factors identified
- Risk factors compared for significance by univariate and multivariate analysis

# UK study of risk factors:

Maclean PS et al. Haemophilia (2010)

- Risk factors for inhibitor development included:
  - Major defects in FVIII gene
  - Non-Caucasian ethnicity
  - High intensity treatment
- No association was found between inhibitor development and the following:
  - Age at first exposure
  - Type of factor VIII product

ORIGINAL ARTICLE

# Rate of inhibitor development in previously untreated hemophilia A patients treated with plasma-derived or recombinant factor VIII concentrates: a systematic review

A. IORIO,\* S. HALIMEH,† S. HOLZHAUER,‡ N. GOLDENBERG,§ E. MARCHESINI,\* M. MARCUCCI,\* G. YOUNG,¶ C. BIDLINGMAIER,‡‡ L. R. BRANDAO,§§ C. E. ETTINGSHAUSEN,¶¶ A. GRINGERI,\*\* G. KENET,\*\* R. KNÖFLER,††† W. KREUZ,¶¶¶ K. KURNIK,‡‡ D. MANNER,†† E. SANTAGOSTINO,\*\* P. M. MANNUCCI\*\* and U. NOWAK-GÖTTL††

**Summary.** *Background:* Different rates of inhibitor development after either plasma-derived (pdFVIII) or recombinant (rFVIII) FVIII have been suggested. However, conflicting results are reported in the literature. *Objectives:* To systematically review the incidence rates of inhibitor development in previously untreated patients (PUPs) with hemophilia A treated with either pdFVIII or rFVIII and to explore the influence of both study and patient characteristics. *Methods:* Summary incidence rates (95% confidence interval) from all included studies for both pdFVIII and rFVIII results were recalculated and pooled. Sensitivity analysis was used to investigate the effect of study design, severity of disease and inhibitor characteristics. Meta-regression and analysis-of-variance were used to investi-

incidence rate was 9.3% (6.2–13.7) for pdFVIII and 17.4% (14.2–21.2) for rFVIII. In the multi-way ANOVA study design, study period, testing frequency and median follow-up explained most of the variability, while the source of concentrate lost statistical significance. It was not possible to analyse the effect of intensity of treatment or trigger events such as surgery, and to completely exclude multiple reports of the same patient or changes of concentrate. *Conclusions:* These findings underscore the need for randomized controlled trials to address whether or not the risk of inhibitor in PUPs with hemophilia A differs between rFVIII and pdFVIII.

**Keywords:** factor VIII concentrates, hemophilia A, inhibitor development, previously untreated patients, systematic review.

# Analysis undertaken:

Iorio A et al. J. Thromb. Haemostasis 8: 1256-1265 (2010)

- Systematic review incidence rates of inhibitor development
- Explore influence of study and patient characteristics
- 2094 patients from 24 studies investigated:
  - 1167 treated with plasma-derived products
  - 927 received recombinant products
- No clear difference identified (“It is not possible to either prove or disprove the hypothesis that there is a higher risk of inhibitor development associated with the use of recombinant factor VIII...”)

# Prophylaxis may prevent inhibitor development:

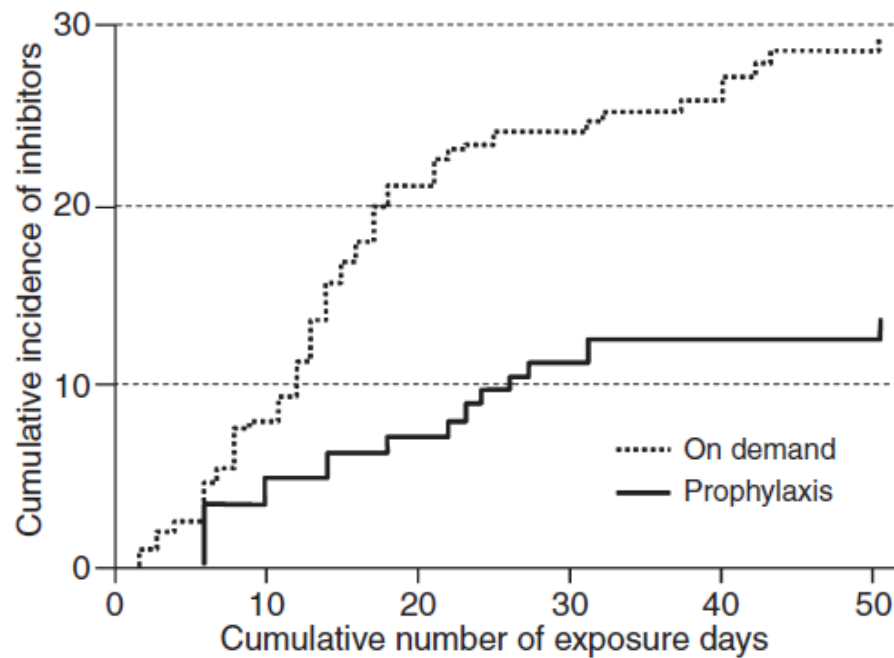


Fig. 1. Cumulative incidence of inhibitor development in previously untreated patients with haemophilia A in the CANAL cohort study: prophylaxis vs. on-demand treatment. This research was originally published in Blood. [15] Copyright American Society of Hematology.

# Importance of “danger signals”:

Brown BD & Lillicrap D. Blood 100: 1133-1140 (2002)

- Presence of active inflammation or activation of immune system makes immune response to new external antigen more likely
- Antigen presenting cells migrate into peripheral tissues in such circumstances and cytokines also promote lymphocyte responses
- Relevant conditions in haemophilia might include: infection; vaccination; trauma; massive muscle bleed; intensive treatment for surgery

# Early tolerization with a low-dose factor VIII significantly reduces inhibitor formation

Kurnik K et al. Haemophilia 16: 256-262 (2010)

	Standard dose regimen (n=30)	Early low-dose regimen (n=26)	P value
Inhibitors	14 (47%)	1 (3.8%)	0.0003 OR 0.048 (95% CI 0.001-0.372)
High responders	8 (27%)	0	0.005
Low responders	6 (20%)	1 (3.8%)	OR of high response 0.00 (95% CI: 0.00-0.57)

**The cumulative inhibitor incidence in the early low dose regimen was reduced by 95% (OR 0.048) compared to the standard regimen**

## Summary regarding recombinant factor IX:

- Long track record of use since licensure in 1997
- Only one brand: monopoly has kept price high compared to plasma-derived equivalent
- Risk of inhibitor development definitely not increased compared to plasma-derived products
- Reduced bioavailability compared to plasma products
- Excellent track record with regard to allergic reactions and thrombogenicity
- Optimal product for the treatment of haemophilia B

# Novel products:

- Clinical trials have already begun and more planned to start soon
- Development wholly based on recombinant technology
- Products under development include:
  - Long-acting factor VIII
  - Long-acting factor IX
  - Long-acting activated factor VII
  - Anti-TFPI antibodies
  - Hybrid human/porcine FVIII for patients with inhibitors
  - Transgenic factor VIII and IX manufactured using animals
- I believe at least some of these products will be available within 5 years

# Comparison between pegylated factor IX and conventional FIX products:

PK Parameters	N9-GP Mean (N=15)	rFIX Mean (N=7)	pdFIX Mean (N=8)	Ratio N9-GP/FIX
$t_{1/2}$ (hours)	92.7	19.3	17.8	5.00
Incremental Recovery (U/dL per U/kg)	1.33	0.69	1.12	1.53 (1.94 ; 1.20)*
CL (mL/hour/kg)	0.70	6.99	5.48	0.11
$V_z$ (mL/kg)	94.2	195	141	0.57
Time to 1% activity (days)	22.5	4.5	4.0	
Time to 3% activity (days)	16.2	2.8	2.7	

Negrier C et al. *Blood* 118: 2695-2701 (2011)

# Dublin Consensus Statement 2011

Vox Sanguinis August 2011

“Patients whose continued health is dependent on the use of blood components or plasma-derived medicinal products have a right, through their representative organisations, to be consulted on any issue which may have an impact on the safety, efficacy or supply of the treatment they receive. Health authorities should ensure that robust mechanisms are in place to ensure that this happens.”

# Personal opinions (1):

- National tenders have proven very effective in reducing the cost of coagulation factor concentrates:
  - Also encourages collaboration between centres
- If price constraint is an issue, better to buy plentiful supply of good plasma products than a limited amount of recombinant products
- Way concentrates are used in clinical practice is more important than type of product:
  - Initial aim is to ensure adequate on-demand treatment (supply in range of 1-2 units FVIII/capita should suffice initially)
  - Next steps should be to develop home treatment and then introduce prophylaxis

## Personal opinions (2):

- Best to have national policy on treatment:
  - Availability of much better treatment in one city or hospital typically results in conflict
- Patient views should be taken into consideration with regard to major policy decisions on treatment
- One option often adopted is to introduce recombinant products in a stepwise fashion, giving priority to PUPs and young children first:
  - Additional benefit of small diluent volume (2.5-5 ml) of recombinant products facilitates infusion in this group

## Personal opinions (3):

- Not always feasible or ethical to wait for results from randomized controlled clinical trials:
  - SIPPET study likely to take several years to complete
  - Other past examples where ethical issues applied include HIV and heat treatment & prophylaxis
  - Patient choice must not be disregarded
  - Reality is no-one in Western Europe is switching back to plasma products in meantime
  - Perfectly acceptable to take into consideration results of non-randomised studies as well as accumulated experience and simple common sense

# Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell



Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

## Abstract

**Objectives** To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

**Design** Systematic review of randomised controlled trials.

**Data sources:** Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

**Study selection:** Studies showing the effects of using a parachute during free fall.

**Main outcome measure** Death or major trauma, defined as an injury severity score  $> 15$ .

**Results** We were unable to identify any randomised controlled trials of parachute intervention.

**Conclusions** As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

BMJ 327: 1459-1461 (2003)