Assessment of long term safety and efficacy of clotting factor concentrates

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Disclosures for: Alfonso Iorio

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SHAREHOLDER	
HONORARIA	Bayer, Baxter, Biogen Idec, CSL, NovoNordisk, Octapharma, Pfizer – No conflicts
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Assessment of long term safety and efficacy of clotting factor concentrates

- Vision
- A few key technical aspects
- State of the art
- Future perspectives

Assessment of long term safety and efficacy of clotting factor concentrates

- Vision
  - Safe, effective, convenient and affordable treatment for as many patients as we can wherever they happen to be born
- Technical aspects
- State of the art

Assessment of efficacy and safety

- Setting the stage:

① Efficacy and effectiveness

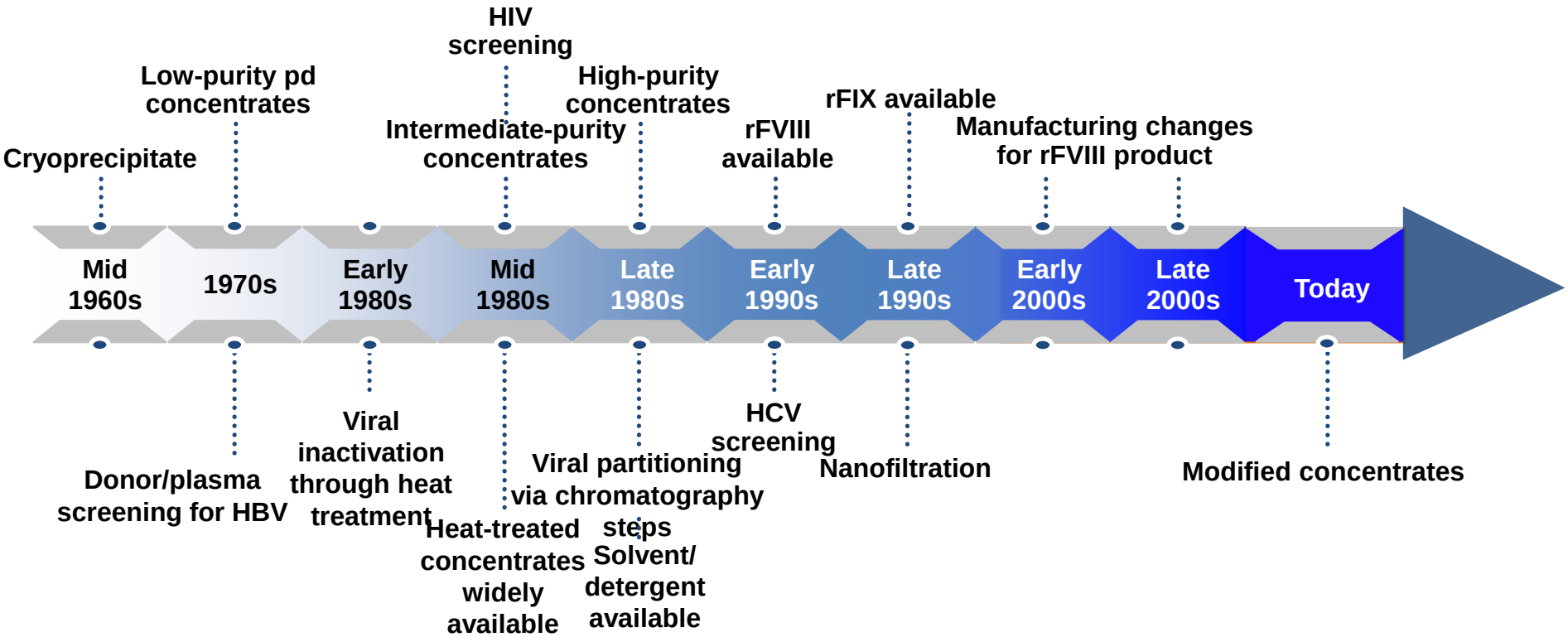
① Long versus short term

① Absolute versus relative

① Concentrates versus regimens

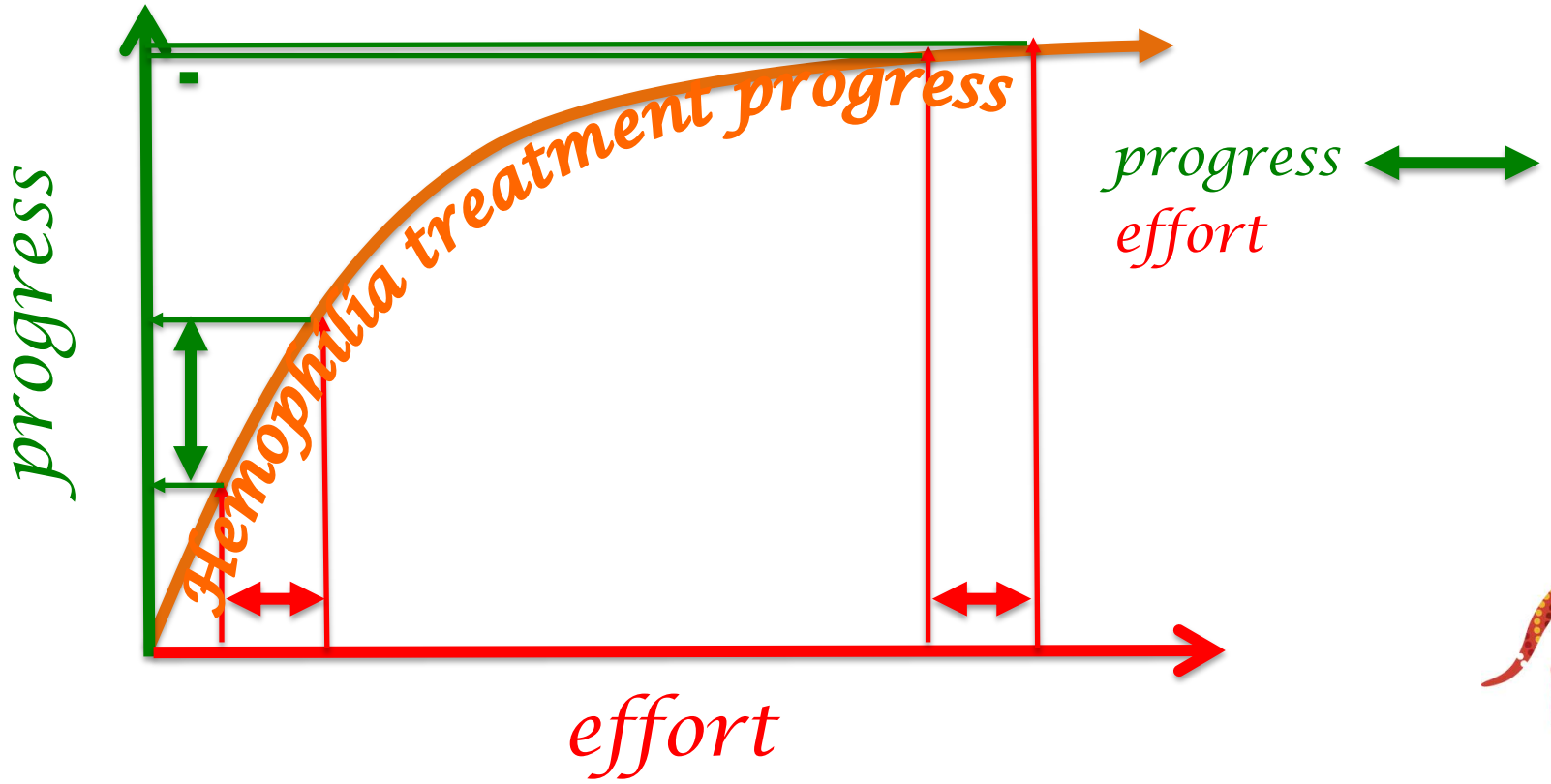
① Individuals versus populations

Haemophilia Product Development



Adapted with permission from Key NS, et al. **1.** Key NS, et al. *Lancet.* 2007;370:439–448.

A more realistic representation..




collectSPACE

The reality is slightly different..

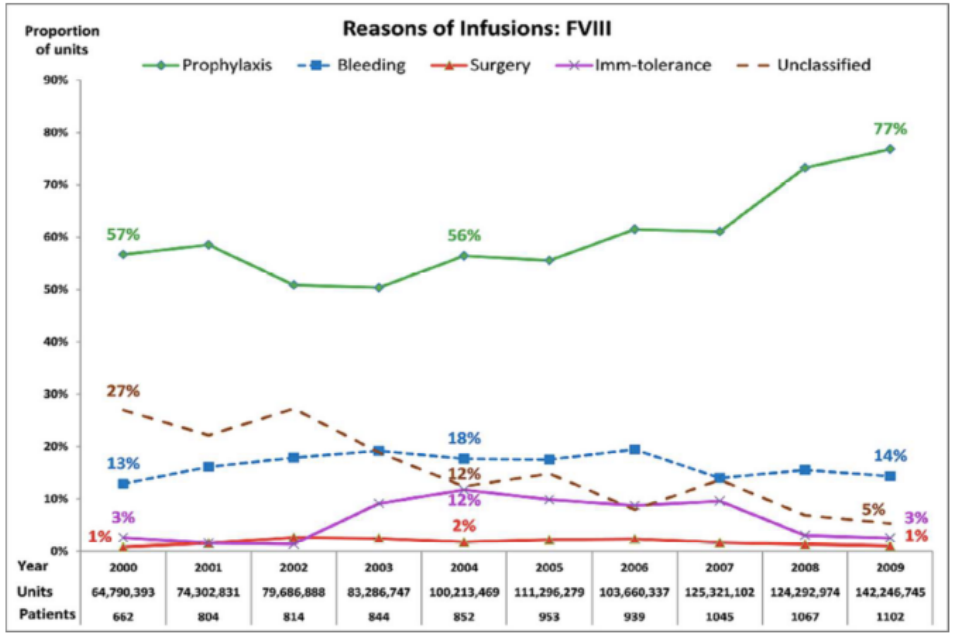
- Study design
- Study setting
- Study size
- Outcome measure(s)
- Comparator(s)

Study design

- Administrative databases
  - National health care systems / insurance databases
  - Disease registry
- Dedicated research databases
  - Prospective targeted research projects

- Comprehensiveness
- Risk of bias reduction techniques

Canadian Hemophilia Assessment Resource Management System (CHARMS)



Over 10 years

- 2260 patients
- FC units tracked
- FVIII: 1 009 097 765
- FIX: 272 406 859

Traore, A et al. First analysis of 10 years trends in national factor concentrate utilization in Canada. Hemophilia, 2014, accepted

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The EUHASS study

- **Strengths**
  - Prospective, very large inception cohort
  - Controlled (parallel, head-to-head)
- **Limitations**
  - Minimal information collected
  - No multivariable approach
  - Confounding still possible
  - Dynamic cohort not always at steady-state

EUHASS: Inhibitors in PTPs

Product	Inhibitors	Pt/yr	Rate	(95% C.I.)
1	5	4656	0.11	(0.03-0.25)
2	1	1987	0.05	(0.00 - 0.28)
3	6	3519	0.17	(0.06 - 0.37)
4	3	2338	0.13	(0.03 - 0.37)

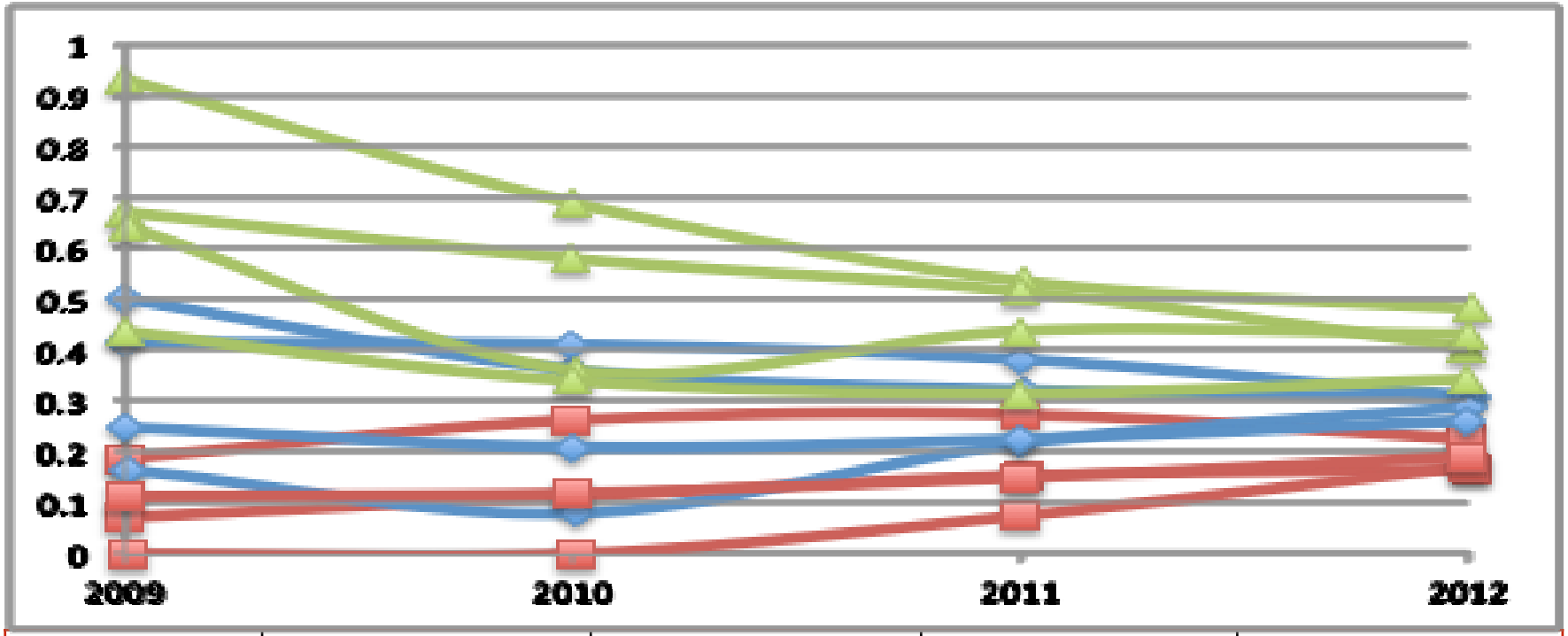
Data from the EUHASS annual reports to the Investigators

Inhibitor rates, selected recombinant FVIII

Product	Studies	Rate (x 100 py)	95% CI
Advate	9	0.10	0.05-0.18
Kogenate	9	0.12	(0.04-0.33)*
Refacto	8	0.19	0.11-0.34
PD factor VIII	4	0.09	0.02-0.45

* 0.26 (0.16 - 0.44) at fixed effect model

Xi, M et al. Journal of Thrombosis and Haemostasis : JTH, 2013; 11(9), 1655–62.



Year	2009	2010	2011	2012
Inhib	8	34	63	96
Exposed	59	121	221	336
Proportion	**0.31**	**0.28**	**0.29**	**0.29**

Data from the EUHASS annual reports to the Investigators

	EUHASS			EUHASS -RODIN		
	P	LCI	UCI	P	LCI	UCI
Plasma D	0.22	0.11	0.35	0.21	0.10	0.37
Recomb	0.26	0.22	0.31	0.24	0.19	0.29
A	0.26	0.19	0.34	0.26	0.17	0.36
B	0.32	0.18	0.50	0.33	0.18	0.52
C	0.30	0.22	0.40	0.22	0.13	0.33
D	0.29	0.17	0.43	0.27	0.15	0.43

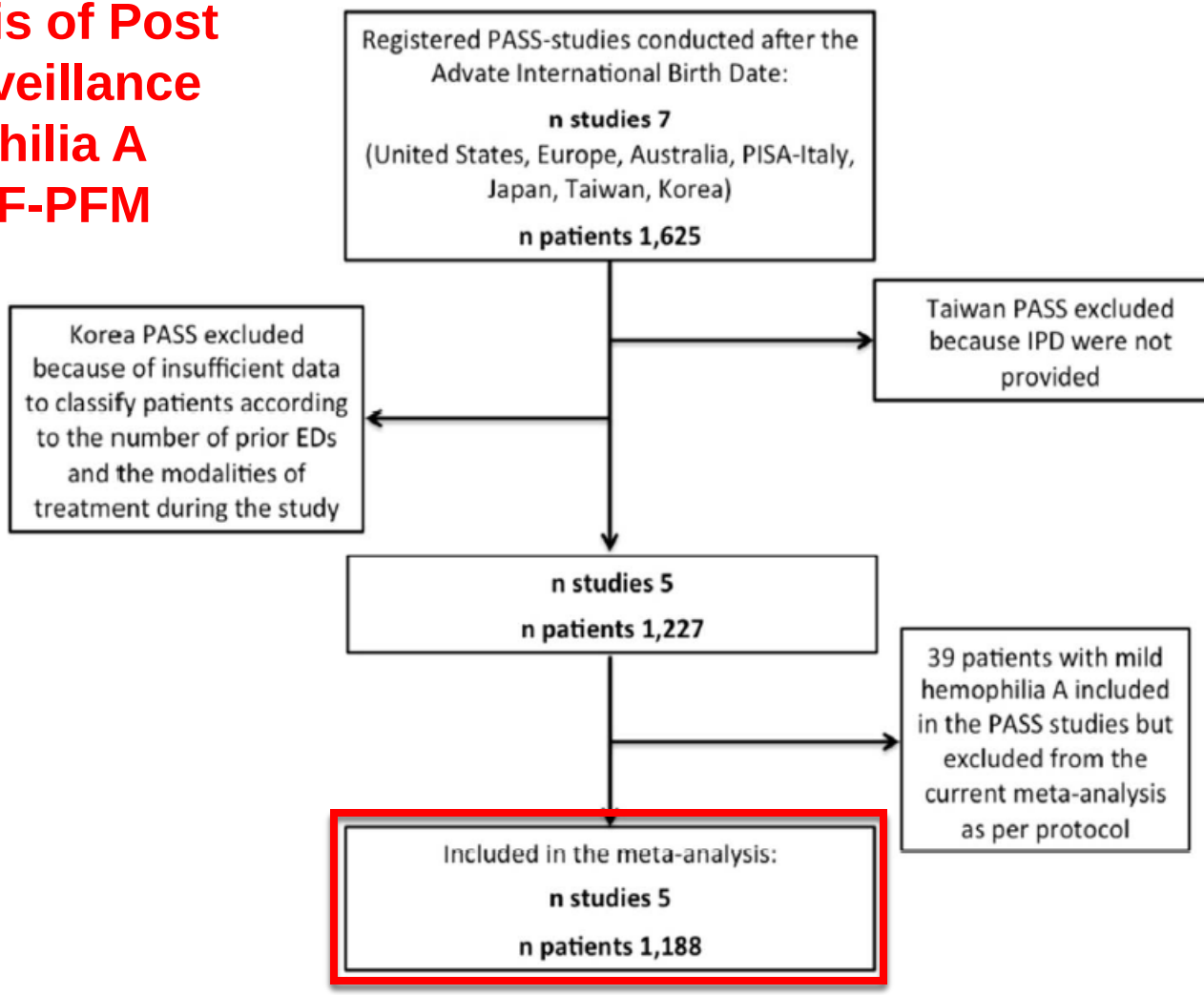
Stakeholders and barriers

- Manufacturers
  - Accessibility to data – comparative effectiveness
- Patients
  - “Disease” denial – burden of data generation
- Treaters
  - Time commitment – applied science
- Researchers
  - Small return

Patient data meta-analysis of Post Authorization Safety Surveillance (PASS) studies of hemophilia A patients treated with rAHF-PFM

Iorio, Marcucci, Cheng, Romanov, Thabane. Hemophilia, submitted.

Study	Patients (n 1,188)
Australia-PASS	34 (2.9)
Europe-PASS	419 (35.3)
Japan-PASS	361 (30.4)
Italy-PASS	281 (23.6)
US-PASS	93 (7.8)



Patient Characteristics & ABR

Characteristics, n (%)	Num (%)	ABR
>150 previous EDs	1016 (85.5)	
Prophylaxis at enrolment	743 (62.6)	
≥ twice/week during the study	587 (49.4)	
Characteristics, n (%)	**Num**	**Median (Q1, Q3)**
All patients	1,140	3.83 (0.60, 12.90)
On demand at enrolment	421	10.38 (2.27, 27.29)
On prophylaxis (on study, any frequency)	710	2.00 (0, 6.73)
On prophylaxis (on study, ≥twice/week)	557	1.66 (0, 4.78)

Median dose per infusion of 27 IU/kg (Q1 20, Q3 34).

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Effectiveness outcomes

- Cure (as a synonym for normal life)
  - Healthy functional joints
    - Bleeding (annualized bleeding rate)

      – Pain
      – Working capability
      – School attendance

Ways to higher effectiveness

- Improving concentrates
- Improving adherence
- Reducing cost
  - Tailoring dose
- Simplifying treatment
- Investigating social and cultural components

Safety outcomes

- Inhibitor development
  - Laboratory variability
- Blood borne infections

- Unexpected events
  - Long term toxicity of modified molecules
  - Drug interactions
  - “Clots”?

Safety outcomes

Inhibitor event rate in PTPs – so what?

As a result of our systematic review, we identified:

- **39 de novo inhibitors** reported in **19 publications.**

Individual patient data has been collected for:

- **29 (74%) inhibitor cases overall**
  - **14 (36%) from CRFs** completed by study investigators
  - **15 (39%) extracted** from patient-level information available in the published reports.

Interim results – inhibitor characteristics

Characteristic (n = 29)	Estimate
Age at inhibitor diagnosis (years)	?
Peak titre level (BU/ml)	??
Last know titre level (BU/ml)	???
Patient follow-up (mo)	????

Barbara,A. Care until Cure grant competition, CHS

Paradigm shift in trial design

- Powell, J et al. *Thrombosis and Haemostasis*, 2012; *108*(5), 913–22
  - Efficacy and safety of prophylaxis with once-weekly BAY 79-4980 compared with thrice-weekly rFVIII-FS in haemophilia A patients. A randomised, active-controlled, double-blind study..
- Valentino, L et al. *JTH*. 2012; *10*(3), 359–67.
  - A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management.
- Manco-Johnson, MJ et al. *JTH*, 2013; *11*, 1119–1127.
  - Randomized , controlled , parallel-group trial of routine prophylaxis vs . on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART).
- Valentino, L et al. *Haemophilia.* 2014; *20*(3), 398–406.
  - Multicentre, randomized, open-label study of on-demand treatment with two prophylaxis regimens of recombinant coagulation factor IX in haemophilia B subjects.
- Antunes, SV et al. *Haemophilia*, 2014; *20*(1), 65–72.
  - Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors.

Long term comparison of different regimens

	NL Median (IQR)	SW, Median (IQR)	P
Joint bleeds, 5 yr	10 (4 -18)	2.5 (0.-9.3)	<.01
Nr joints	2 (1-4)	3 (2-3)	.47
HJHS (max144)	9.0 (2.0 – 18.)	4.0 (2.0 – 6.0)	<.01
Activity (max 100)	93 (81-98)	99 (93-100)	<.01
EQ-D5 utility	0,04 (0.81 – 1.00)	1.00 (0.81 – 1.00)	.93
Factor cost	851 (647-1048)	1474 (1154-1778)	<.01
Lost production	0 (0-0)	0 (0-0)	.82

Fischer, K et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s. Blood, 2013; 122(7), 1129–36.

New study design

- Interrupted time series
  - Ramsay, C. R. et al. *Int J Technol Assess Health Care*, 2003;*19*(4), 613–23.
- Paired availability design
  - Baker, S. G. et al. *BMC Med Res Method*, 2001;*1*, 9.
- Randomized registry trial
  - Lauer & D'Agostino *NEJM* 2013;*369*(17), 1579–81.

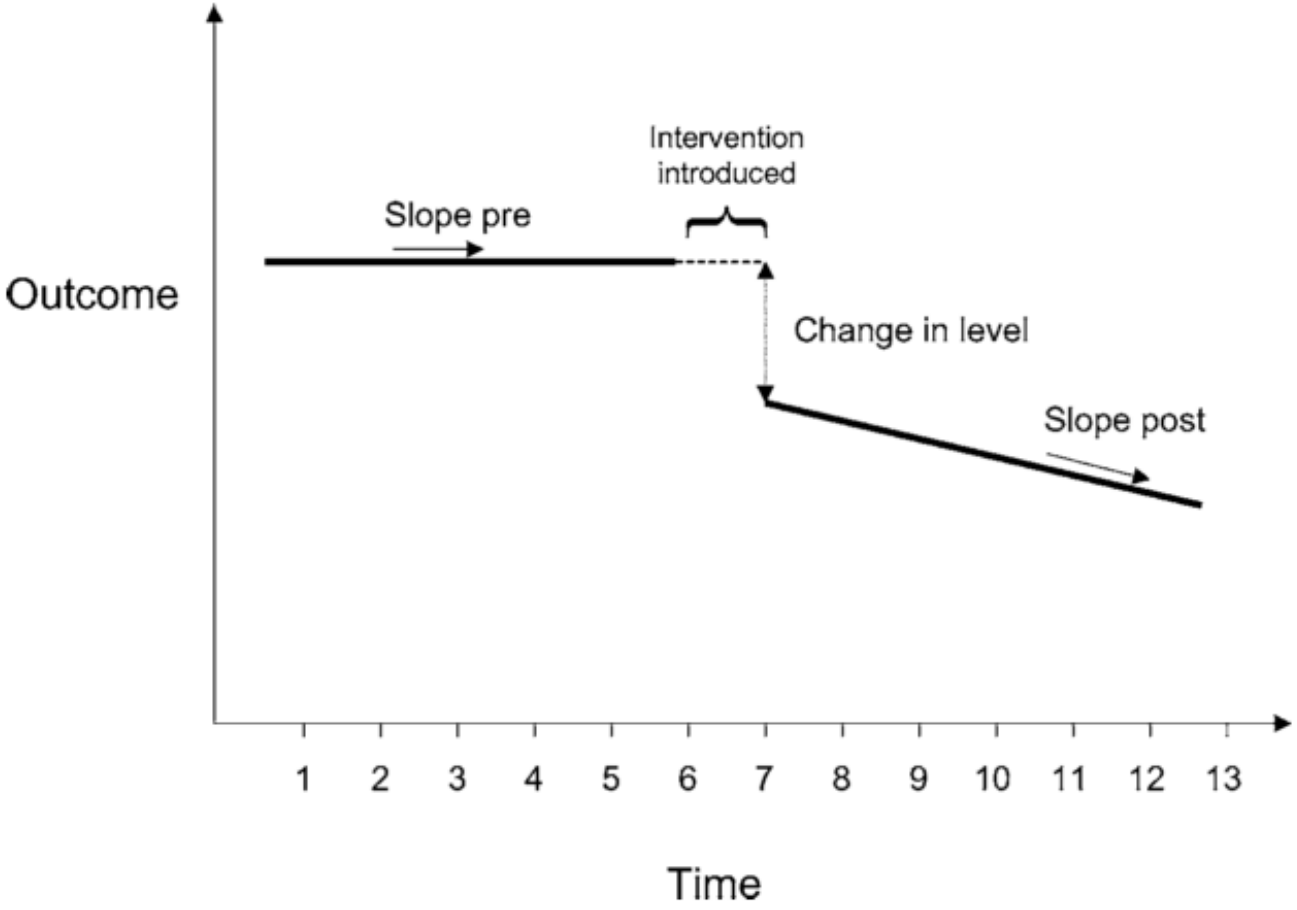
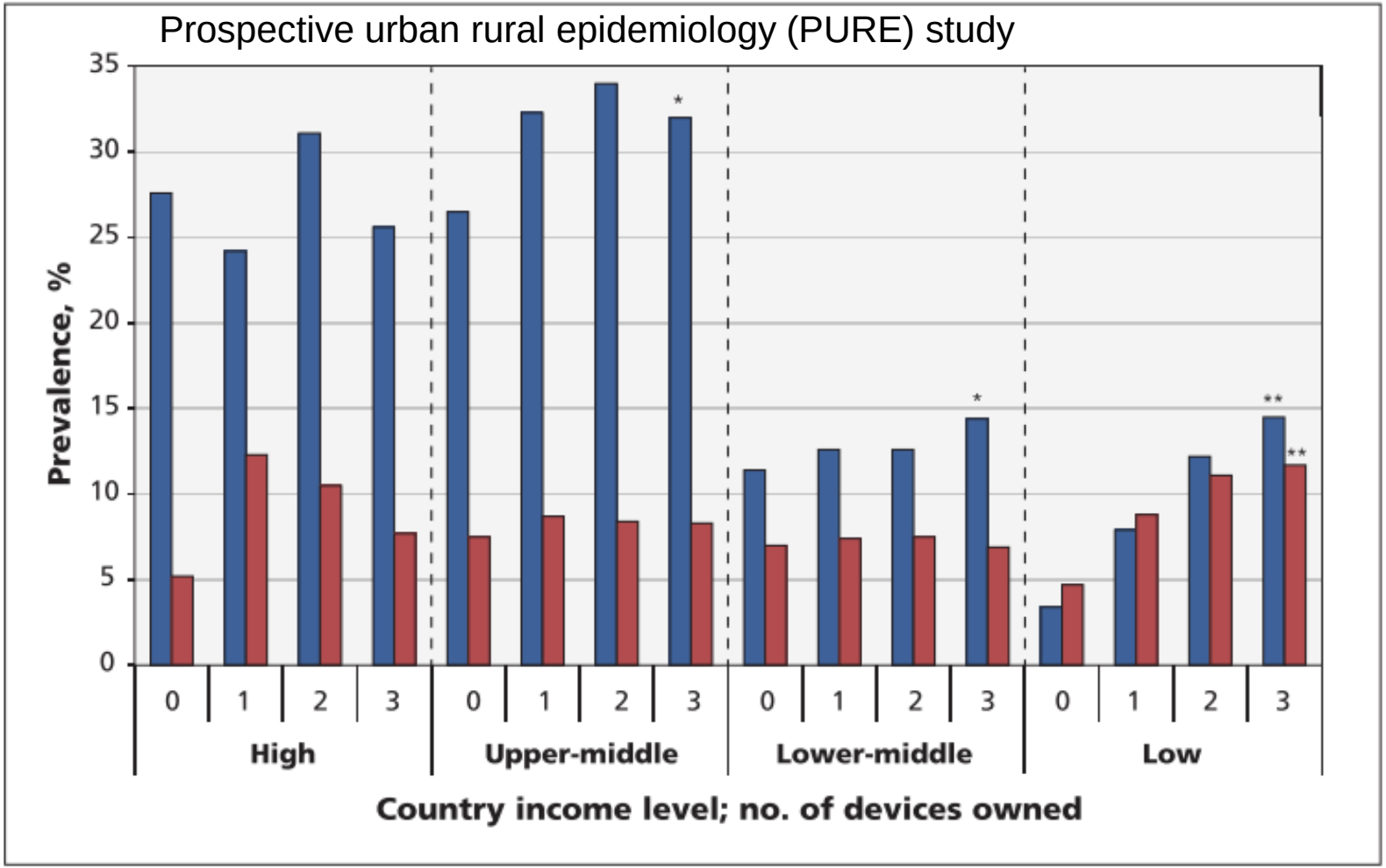


Figure 1. The effect sizes estimated by time series regression analysis of an interrupted time series design.



Lear, S. A. CMAJ, 2014 186(4), 258–66.

Innovation

- Bailey, SD. Diabetologia, 2014,57;4:738-45

- Huffman, MD and Yusuf, S. JAMA. 2014,63;14:1368-70

Conclusions

- Clear need for surveillance
- Clear evidence of progress
- Need for harmonization
- Need for guidance

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Thanks

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