

The role of medical societies in promoting good practice and the scope for reprovigilance

Roy G Farquharson

MD FRCOG

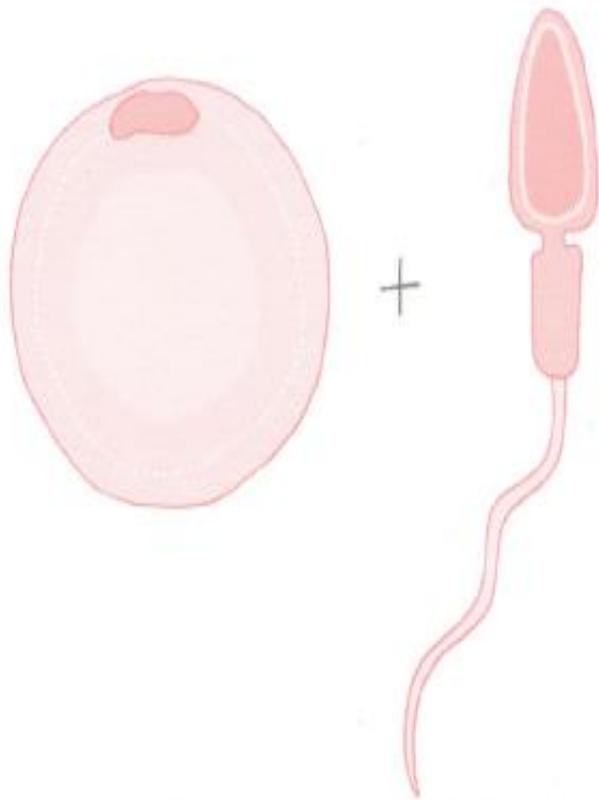
Liverpool Women's Hospital, UK

Contact: rgfarquharson@yahoo.com



Declaration of Interests

- Past Chair, European Society of Human Reproduction and Embryology (ESHRE) (2019-2021)
- NICE Guideline Development Group (CG 154, 2010-2013)
Evidence Update Advisory Group, 2014
- Chair, Association of Early Pregnancy Units (2006-2011)
- ESHRE Executive Committee Chair (2017 - 2019),
Chair-elect (2015 – 2017), ExCo Member (2011-15),
Co-ordinator, Special Interest Group for Early Pregnancy
(2007-2010)
- Associate Editor, Human Reproduction Update
(2010-2014)
- No conflict of interest to declare



they did it!

The ESHRE Mission

May your single embryo transfers
be increasingly successful

ESHRE ART map of Europe in 2014

In 2014 survey, the European IVF Monitoring group (EIM) covers nearly 80% of European countries with ART activity



Countries	36
Centers	1,184
Cycles	707,171
Children	146,232

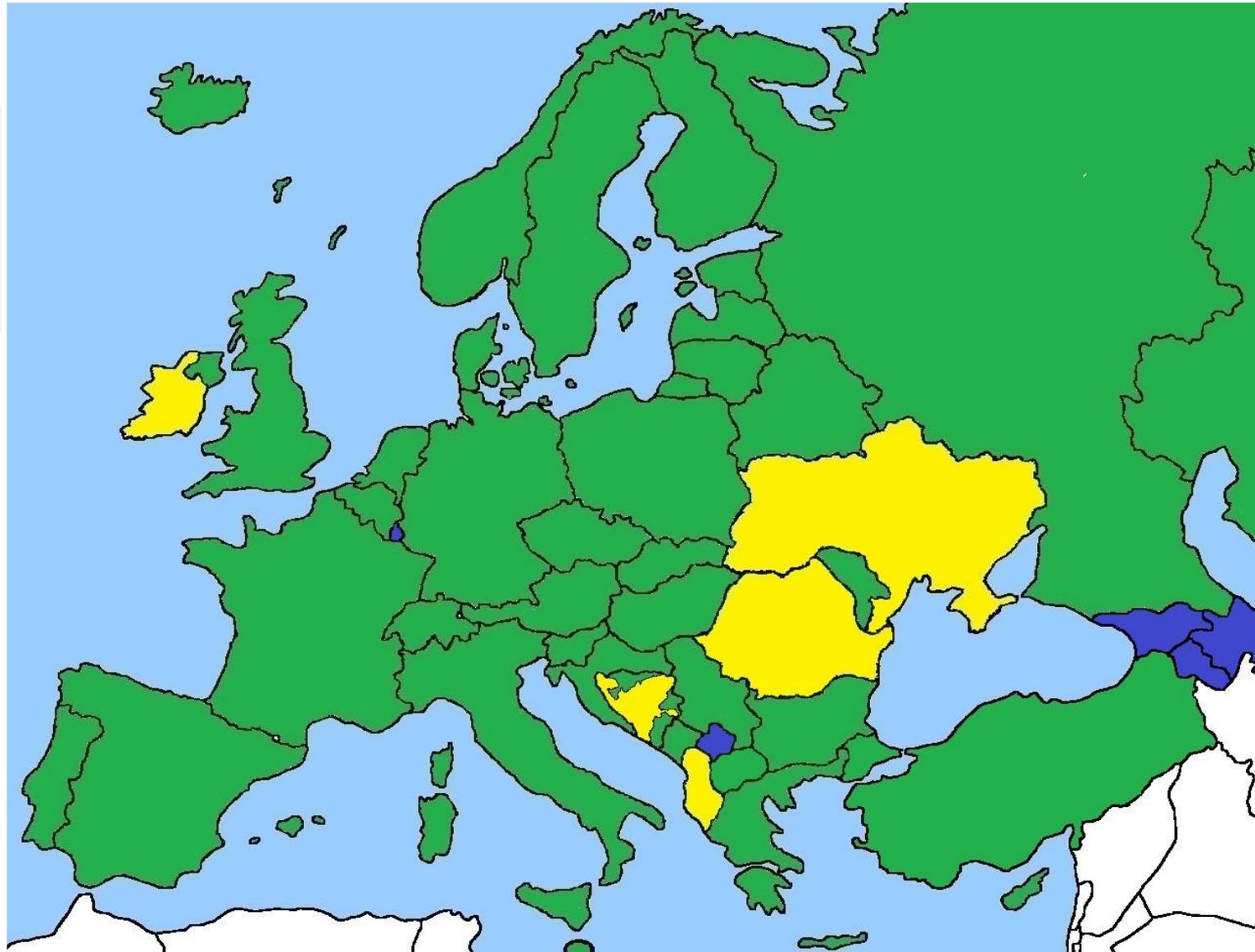
Diversity is the European Paradigm - Survey on ART in Europe

Main areas:

- **Availability (ART legislation)**
- **Accessibility – legal criteria**
- **Accessibility - funding/reimbursement**
- **Non-partner donation**
- **Registers**

National MAR (ART) Legislation reflects the national culture

Countries with specific ART legislation



Countries	Is there a specific ART law?	Infertile heterosexual couples	Single women	Female couples	Male couples
Albania	+	●●●●●●●			
Austria	+	●●●●●●		●●●●●●	
Belarus	+	●●●●●●●	●●●●●●●		
Belgium	+	●●●●●●●	●●●●●●●	●●●●●●●	●●●●●●●
Bulgaria	+	●●●●●●	●●●●●●	●●●●●●	
Croatia	+	●			
Cyprus	+	●●●●●●●	●●●●●●●		
Czech Republic	+	●●●●●●●			
Denmark	+	●●●●●	●●●		
Estonia	+	●●●●●●●	●●●●●●●		
Finland	+	●●●●●●●	●●●●●●●		
France	+	●●●●●●			
Germany	+	●●●●	●●		
Greece	+	●●●●●●●	●●●●●●●		
Hungary	+	●●●●●●●	●●●●		
Iceland	+	●●●●●●	●●●●●●	●●●●●●	
Ireland	-	●●●●●	●●●●●	●●●●●	
Italy	+	●●●●●●			

- IVF/ICSI with own gametes
- IVF/ICSI with sperm donation
- IVF/ICSI with egg donation
- IVF/ICSI with sperm and egg donation
- Embryo donation
- PGD
- PGS
- Surrogacy

ACCESSIBILITY - public funding/reimbursement

Is there a limited no. of funded cycles?

Yes, in 32 countries:

1 (2 countries)

up to 5 for first child + 4 for the second one (1 country)

3 cycles (15 countries) – most frequent

Are all ART techniques publicly funded?

Yes, in 18 countries

Are ART techniques publicly funded in a consistent manner within the country?

No, in 16 countries

Is it possible to claim tax deductions for ART expenses?

Yes, in 10 countries

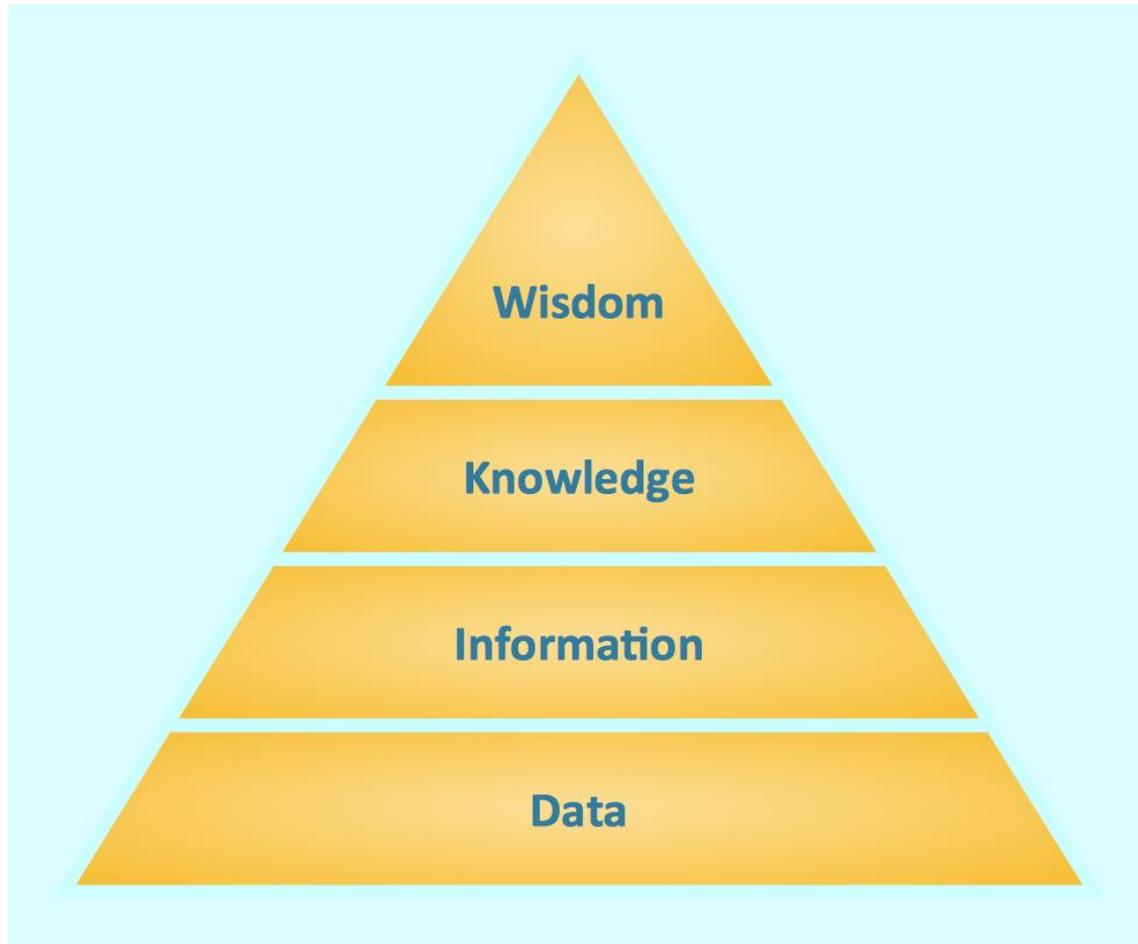
Overview

- **Diversity is the European paradigm**
- **Funding/reimbursement is extremely variable**
- **Non-partner donation is culturally dependent**
- **Effective and more robust registers are needed**

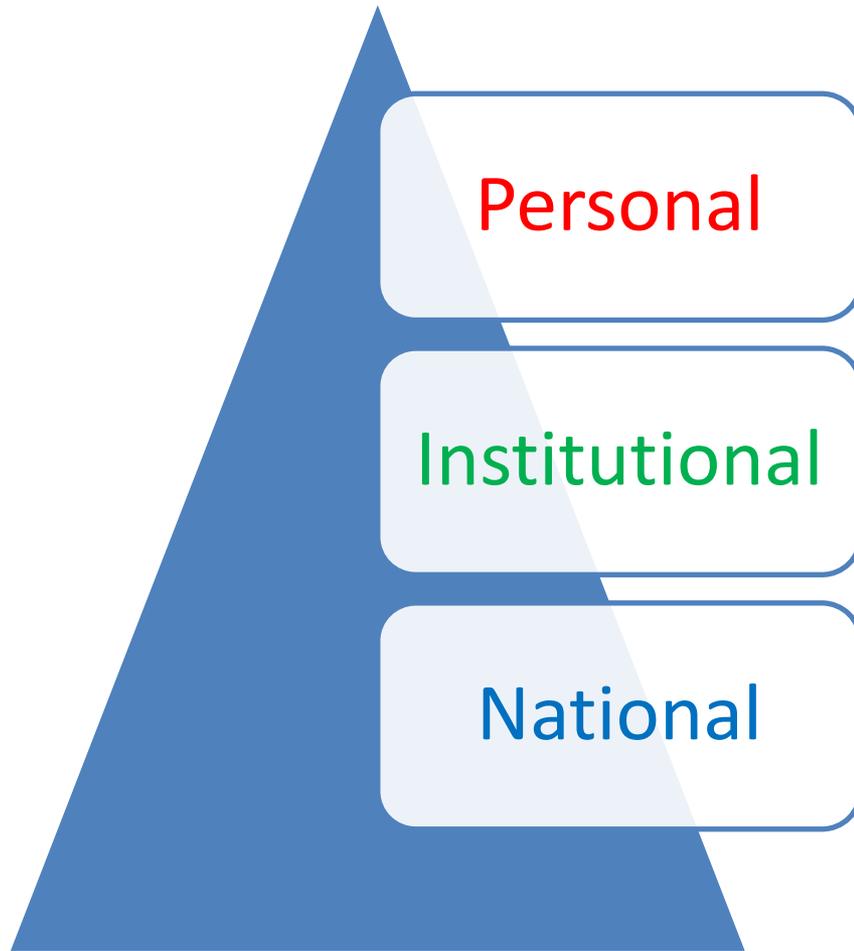
National legislation changes with elections (2018)

eg more restriction in Poland, Swiss referendum vote for MAR

Hierarchy of Enlightenment



Individual Hierarchy of Participation



- Moral alertness; CME compliance; commercial influence and self; ethically approved studies
- LREC/MREC approval; governance structure and function; leadership veracity; responsiveness to concerns/identified problem
- Ethical structure/function; patient safeguarding; regulatory agencies;

Medical Societies – where are we?

- ‘Limiting’ the use of unfounded techniques and pressure from commercialisation is incompatible with existing culture and practice
- Patient safeguarding and robust mechanisms for vigilance surveillance are few
- Public engagement via patient organisations within research is novel and not universally encouraged nor respected
- Verification and validation of new ART treatments is rapidly developing and needs an objective framework of assessment

ESHRE Strategy Meeting on Commercialisation

Brussels

18/19th February 2016



Modifying the Effects of Commercialisation

- Maintaining scientific integrity – the challenge to ESHRE
- Avoiding practice bias and financial profiteering for personal gain
- Vigilance and scrutiny – how to implement, develop and sustain correct processes
- Creating Gateways eg Trials Registration and future publication
- ESHRE policy and practice encourages – identifying knowledge gaps, design, standards, recruitment, ethical & GCP compliance

Boundary between ESHRE and Companies

- Acknowledging compliance rules and implementation at Annual Meeting and setting ESHRE Standards
- EU Pharma rules, ESHRE self regulation, Policing of responsibility level variable
- Company Symposia – their place, structure, content, interaction with ESHRE delegates
- Exhibition Area – Commercial area boundary made obvious with HCP v non-HCP entry

Collaborating in Constructing a Regulatory Framework

- Making a start and adapting current personal DOI form that is fit for purpose applied to all ESHRE office holders and initiate compliance check system
- Base concepts and practice on existing ESHRE paper by SIG's E&L and SQART:
'Beyond the dichotomy: a tool for distinguishing between experimental, innovative and established treatment' Provoost V et al. *Hum Reprod* 2014; 29(3):413-417
- Co-signatory to HFEA Add-ons Consensus statement in 2018 and promotion of Traffic Lights System of EB Practice

Priorities and Principles

- **Transparency and clear disclosure**
- **Accessibility to data and study design**
- **High quality data**
 - **Randomized clinical trial**
 - **Double-blinded (placebo control where feasible)**
 - **(Unchanging) clinically meaningful endpoints**
 - **Reasonable duration of long term follow up**
- **Safety and effectiveness**
- **Post market data collection – registry, etc.**

Big Data (Keynote Lecture at ESHRE 2020) and Reproducibility in Reproduction

- Does the source of funding affect the result?
- Large scale analysis of published studies demonstrates a **variable** outcome difference
- 96% of Commercial sponsorship studies are associated with **significant** results
- Public funded studies (eg US NIH, UK HTA) are associated with high levels of negative, **non-significant** results (*approx 10% positive*)
- *Bibliography:*
 - Ioannidis JP. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. *Milbank Q.* 2016a;94:485-514.
 - Ioannidis JP. Why most clinical research is not useful. *PLoS Med.* 2016c,13:e1002049.
 - Ioannidis JPA, Stuart ME, Brownlee S, Strite SA. How to survive the medical misinformation mess. *Eur J Clin Invest* 2017;**47**:795-802.

Pharma funded RCT

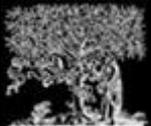
Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: a double-blind, randomized, parallel, placebo-controlled trial

Ashok Kumar, M.D., Ph.D., Nargis Begum, M.Sc., Ph.D., Sudha Prasad, M.D., Sarita Aggarwal, M.D., Shashi Sharma, Ph.D.

Fertility and Sterility

Volume 102, Issue 5, Pages 1357-1363.e3 (November 2014)

DOI: 10.1016/j.fertnstert.2014.07.1251



Not all Pharma funded RCT's are positive

Recombinant human granulocyte– colony stimulating factor in women with unexplained recurrent pregnancy losses: a randomized clinical trial

A Eapen M Joing P Kwon J Tong E Maneta C De Santo F Mussai D Lissauer D Carter

Human Reproduction, **2019**, 34, 424-432

SUMMARY ANSWER: rhG-CSF administered in the first trimester of pregnancy did not improve outcomes among women with a history of unexplained recurrent pregnancy loss.

Public Funded RCT

Progesterone therapy – no benefit

HEALTH TECHNOLOGY ASSESSMENT VOLUME 20 ISSUE 41 MAY 2016 ISSN 1366-5278

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Promise
Trial 2016

A Randomized Trial of Progesterone in Women with Recurrent Miscarriages

A. Coomarasamy, H. Williams, E. Truchanowicz, P.T. Seed, R. Small, S. Quenby, P. Gupta, F. Dawood, Y.E.M. Koot, R. Bender Atik, K.W.M. Bloemenkamp, R. Brady, A.L. Briley, R. Cavallaro, Y.C. Cheong, J.J. Chu, A. Eapen, A. Ewies, A. Hoek, E.M. Kaaijk, C.A.M. Koks, T.-C. Li, M. MacLean, B.W. Mol, J. Moore, J.A. Ross, L. Sharpe, J. Stewart, N. Vaithilingam, R.G. Farquharson, M.D. Kilby, Y. Khalaf, M. Goddijn, L. Regan, and R. Rai

ESHRE Collaboration

- the virtuous circle of strength



**Scientific
Advance**

**Clinical
Innovation**

**Intellectual
Wealth**

The Scope for Reprovigilance

- The role of specialist medical societies was historically confined to research, education and training for the benefit of its membership. A more modern approach has enlarged that sphere of interest to include core behaviour standards and patient safeguarding.
- With ART specifically in mind, the journey from gamete to child via pregnancy and the newborn requires safety assurance and dialogue with regulatory agencies to protect patients from harm. Reprovigilance is a term coined by ESHRE that involves monitoring of activity and intervention that mirrors the ethos of our core values.
- Motto is 'Creating cohesion and dispelling confusion'

Prevention or Patience?

- “There are events in the womb of time, as yet, undelivered “

from **Othello** (Iago, Act 1 Scene 2)

William Shakespeare