

EDITORIAL



May the colleague who truly has no conflict of interest now please stand up!

Avividly remembered conversation from quite a few years ago with someone influential in Dutch society began 'I am sure you academics do very important scientific work, but the problem is that we as society notice so little health benefits resulting from these discoveries. Since universities are primarily paid by tax payers' money, what's our return on this investment?' It took quite some time to get to grips with this message, but it did lead to the profound realization of how far away from mainstream society we often operate. In the past, clinical researchers essentially decided for themselves which disease condition or intervention to study and what endpoints were considered most important. Usually there was no external scrutiny of research proposals, particularly when external peer-reviewed funding was not required because internal resources were sufficient to perform the study.

This 'ivory tower' approach to determining research priorities has now been completely dismantled, and many stakeholders (often including those representing public and patient involvement) now engage in identifying the most important unmet health needs of society. In most cases, the top-down allocation of research funding is informed by the scrutiny of these needs, in addition to a consideration of the relevance, scientific quality, novelty and feasibility of submitted proposals. Increasingly, other recent developments are empowering patient/ public influence on the way research is carried out, such as value-based healthcare assessment, shared decision making, and patient-reported outcome measures (PROMS)

CONFLICTS OF INTEREST MAY BE EVERYWHERE

The reader may wonder what all this has to do with an editorial addressing conflict of interest? Having left its comfortable position of 'splendid isolation', academia

is now prominently engaged in all sorts of activities considered more relevant to society. These activities often require significant support from external funding bodies, charitable organisations, the pharmaceutical industry, and other commercial partners. Investigators may also start their own spin-off company aiming for greater independency and to attract investment funding. In this complex interplay between different parties, often involving considerable sums of money, it is clear that significant conflicts of interest may arise.

First of all, what constitutes a conflict of interest? Depending on the context, definitions can vary significantly. The most widely used definition, as outlined in *Wikipedia*, describes it as follows: 'A conflict of interest is a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a secondary interest'. For further reading see the commentaries by *Relman, 1984*; *Bekelman, 2003*; *Rosenbaum, 2015a*; *Rosenbaum, 2015b*; *Fontanarosa, 2017*; *Anonymous, 2018*.

Over the years we have witnessed instances of high profile, lay press coverage reporting misconduct among some of our colleagues. Examples have included review papers or consensus statements published in prestigious scientific journals with clear recommendations on the preferred use of specific drugs, in which it later transpired that the authors had failed to declare their financial relationship with the respective pharmaceutical company (<https://www.statnews.com/2016/04/05/new-england-journal-of-medicine-feuds/>). This type of conflict may also emerge in the context of advising on government policies. An illustrative case arose when in 2015 the minister of health in the Netherlands was forced to withdraw her recommendation regarding the use of a vaginal flushing method to replace cervical Pap Smears, after the discovery

that the chair of the health counsel committee advising her was also a shareholder of the company producing the flushing device (<https://www.nrc.nl/nieuws/2015/06/20/onderzoek-naar-kanker-stilgelegd-wegens-verzwegen-belangen-meijer-a1415362>).

Equally well publicised in the past has been the reluctance of investigators or pharmaceutical companies to publish negative data in which no difference in outcome was observed between a novel intervention and the standard care practice. Widespread concern regarding publication bias led to action, and this practice is now largely prevented by the requirement of scientific journals that trials submitted for publication must have been registered in an international trial registry before commencement. However, this does not prevent high impact journals being much more likely to accept a manuscript for publication when a positive difference between the study intervention and the control is reported. While this is normally dismissed as publication bias, it clearly points to a conflict of interest. A negative study showing no difference is just not very sexy, similarly a study that solely confirms previous findings. A chief editor of a journal understand very well that exciting and controversial findings will generate more media coverage and citations, with reliable benefits for the journal's impact factor and visibility. Beyond any doubt, published studies showing no difference in outcome between treatment options should be common, and we now all acknowledge the importance of studies confirming or disputing previous findings since it has been demonstrated that many initial findings cannot be reproduced.

In addition to these 'headline' examples, many less overt potential conflicts of interest have been identified. Perhaps one of the best known relates to the reported impact of the involvement of pharmaceutical companies on the outcomes of phase three clinical trials

(Chew, 2014). Another area of concern that has led to tighter controls in many countries is the influence that the pharmaceutical industry may exert through medical education (Golestaneh, 2017) or its support of patient organisations.

Away from the industry, the peer-review system itself – central to accepting or rejecting submitted manuscripts for publication – is clearly a rich area in which conflict of interest can play out. Peers, often working in the same area of research, evaluating submitted manuscripts may have motives other than the scientific merit of the work for recommending either acceptance or rejection. For sure, the current peer-review system is far from evidence-based.

DISCLOSURE VERSUS CONFLICT OF INTEREST

Many journals have now developed formal procedures that aim to make any potential conflict of interest transparent to the reader. In *RBMO* in the information provided for potential authors it is stated under declaration of interest that 'All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work' (<https://www.rbmojournal.com/content/authorinfo#idp1396336>). Moreover, our journal annually discloses the interests of all editors. Authors are asked to declare their interest and it is up to the editor and reader to decide whether they would consider such interests a potential conflict. Objectively assessing what disclosed interest might constitute a conflict turns out to be rather problematic and is itself open to bias. In our opinion, a pragmatic approach is required that focuses primarily on transparency. In practice, this would require all authors to clearly disclose all their interests (including who is paying their salary) and allow the reader to judge how this disclosure should affect their interpretation of the study findings and recommendations.

However, many of us will have seen instances where an author's declaration of no conflict of interest in relation to a particular study might be questioned by their close and informed peers. This implies a significant level of underreporting.

Given the vast potential for conflict of interest to shape scientific discourse, it is not surprising that many formal bodies have attempted to address this by imposing an ever increasing number of regulations, rendering clinical research more and more difficult, time consuming and costly to perform (Humaidan, 2019)

LESS RECOGNIZED POTENTIAL CONFLICTS OF INTEREST

While most readers will be familiar with the examples discussed thus far, it is useful too to consider possible examples of less conscious conflicts of interest.

Research methodology and its implications: Recently, there has been considerable debate regarding the use and misuse of randomized controlled trials (RCT) (Macklon *et al.*, 2019, amongst many other contributions). There is no doubt that the introduction of evidence-based medicine (EBM) approaches has advanced our field and related patient care, and we have been active exponents of its research methodologies. However, it also needs to be acknowledged that for some EBM is not just seen as a means to reach valid conclusions, but has become a dogma that does not always welcome challenge or criticism (<https://www.medischcontact.nl/nieuws/laatste-nieuws/artikel/groepsbewijs-moet-evidence-voor-individu-woorden.htm>; Macklon *et al.*, 2019). We should appreciate that, particularly in the current era of personalized medicine, other research strategies such as prospective, cohort, follow-up studies in well-characterized cohorts and with well-defined study endpoints may also generate clinically important and scientifically valid 'evidence' (Fauser 2017a; Fauser 2017b).

Some of the drivers for the continued focus on EBM are clear. Large sample size RCT are highly regarded by funding bodies and high impact medical journals, despite sometimes being based on questionable scientific rationale or offering limited clinical relevance. However, other drivers need to be appreciated that might be considered to represent a conflict of interest influencing academic behaviours.

University profiling and individual academic careers: Universities the world over are engaged in an increasingly competitive global and lucrative market

place. As with almost every other aspect of modern life, league tables are published to compare their performance across a range of metrics, ranging from scientific excellence to student-focused teaching. Indeed, most universities now appear able to declare that they are in the 'top 50' for some parameter however arcane it may be (<https://www.thecompleteuniversityguide.co.uk/league-tables>). This requirement puts new pressures on individuals acting within this system aiming for an academic career. National initiatives such as the UK Research Excellence Framework, and its predecessor the Research Assessment Exercise, provide examples of how these pressures apply not only with respect to publications but how they also encompass broader impacts. (<https://www.ref.ac.uk/about/what-is-the-ref>).

Competition for attention by society and the media encourages communication managers to produce press releases often considerably overstating the impact of the scientific work presented, resulting in media attention with juicy headlines which often have very little to do with the study upon which it was based. The scientific impact of this potential conflict of interest risk is that in the eternal struggle for attention we will tend to overinterpret our findings, or seek to find impact even in essentially negative results.

Dealing with interests during conferences: At most scientific conferences these days, speakers are required to include a slide at the outset of their presentation that discloses their interest. Many will feel they have none to declare, as they do not have any paid associations with industry. Others will provide exhaustive lists and perhaps take some comfort from the degree they feel their eminence is recognized beyond the conference room. This is a practice to be welcomed as it serves to offer transparency to the audience as they weigh up how to interpret the findings presented in the same way as they would when reading a scientific publication. However, once the lecture is over and the chair invites questions, transparency can vanish, as the questioner will at most be invited to provide his or her name and country of origin. The opportunity for commercial or personal interest to abuse this situation are clear. There is therefore an opening for any potential conflict of interest to be made similarly transparent for audiences, and a simple task exists

for session chairs to add a request to disclose any interest that might relate to the question or topic when inviting a questioner to speak.

Focus on clinical care versus academic achievement: In the UK the use of so-called 'add ons' in IVF has been heavily debated recently. The use of expensive, but often unproven, added interventions are widespread in couples where previous 'routine' IVF attempts failed. In a commercial environment, financial incentives may represent an important driver of this development and clinicians can easily be accused of exploiting desperate infertile couples who are willing to do everything to get pregnant (Macklon et al., 2019).

However, a conflict of interest may also arise the other way around which is much less recognized. In healthcare systems where most IVF is funded with a fixed fee per cycle, such as in the Netherlands, an opposite incentive for undertreatment exists. Under those circumstances, useful new developments or additional interventions may be denied to couples, since they represent an additional financial burden to the clinic that will not be reimbursed.

The paradox may arise that self-funded patients may be exposed to the risk of exploitation due to unnecessary overtreatment, whereas those receiving

treatment in countries that fund IVF under fixed (and often low) tariffs, rather than being protected, may instead receive suboptimal treatment because of similar, although differently directed, financial considerations.

Whether clinicians and embryologists working in an academic environment focus predominantly on patient care or on research may in itself represent a conflict of interest. Great research may facilitate your academic career, whereas excellent clinical IVF outcomes may be beneficial for your practice and related financial gains in other settings. It has been known for many years that clinical outcomes of IVF (de Geyter et al., 2018) and research output (Aleixandre-Benavent et al., 2015) vary significantly from country to country.

In general, it may be proposed that the quality of clinical care benefits from good research. We explored whether there might be an association between the quality of clinical IVF care on the one hand and research in reproduction output on the other hand (FIGURE 1). Of course such a very preliminary crude analysis has serious limitations and may be influenced by many confounders, but it seems justifiable to conclude that a clear positive correlation between research output and quality of clinical care does not exist for IVF. If anything, a negative association seems more likely,

suggesting that countries with excellent IVF results have relatively poor science output and vice versa. Food for thought, although – of course – these findings should be considered very preliminary and should be explored further.

SOME SUGGESTIONS FOR USEFUL NEXT STEPS

First of all, in keeping with what we outlined earlier, we will disclose our full interests (see below). We leave it up to you the reader to decide whether any of our (many) interests could be considered a potential conflict in relation to this editorial.

- It should be appreciated that a conflict of interest may be present in every step of scientific research, publication and communication. The complete disclosure of interest should also include who pays the salaries.
- We should aim for a focus on the full disclosure of interest of everyone involved in conducting research, rather than overregulating the process. We should acknowledge that every control system can be bypassed and hence a 100% coverage of interest can never be guaranteed. We should move towards a system based on trust rather than distrust.
- We need to challenge the notion that collaboration with industry implies a *de facto* conflict of interest and the

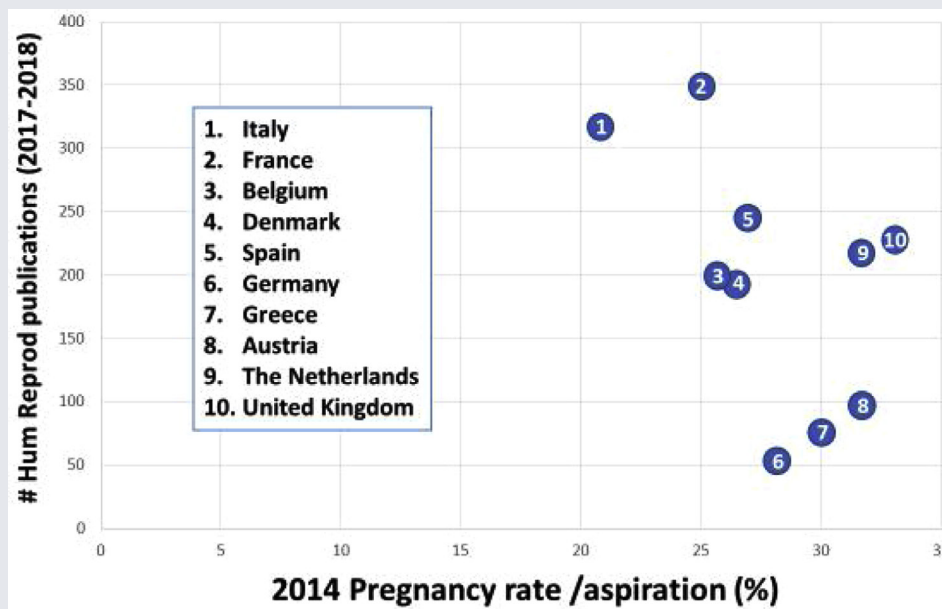


FIGURE 1 Pregnancy rate per oocyte aspiration for 10 European countries for 2014 (from de Geyter et al., 2018) and 'scientific output' per country as measured by the number of papers published in the journal *Human Reproduction* during the years 2017 and 2018 (presumed the years of publication of studies ongoing in 2014), the latter compiled manually from PubMed by BCMF, 20 July, 2019.

similarly erroneous view that those who do not work with industry are by definition free of conflicts of interest. This means that a default position of 'pharmaceutical industry bashing' should be resisted and instead we should aim for transparent and creative partnerships with pharma and other commercial partners.

- We should recognize that both clinical care and research are context-dependant, and include financial and academic drivers.
- We should be open-minded regarding the value of different research strategies, and acknowledge that methods other than EBM may also provide useful information, especially in the context of individualized care.

EXTENDED DISCLOSURE OF INTEREST STATEMENT FROM THE AUTHORS

During the last 4 year period BCJM Fauser has received salary/fees or grant support from the following organisations (in alphabetic order); Abbott, Controversies in Obstetrics & Gynecology (COGI), Dutch Heart Foundation (Hartstichting), Dutch Medical Research Counsel (ZonMW), Ferring, International Federations of Fertility Societies (IFFS), London Women's Clinic (LWC), Menogenix, Myovant, OvaScience, Pantharei Bioscience, PregLem/Gedeon Richter, Reproductive Biomedicine Online (RBMO), Teva/Theramex, University Medical Center Utrecht (UMCU), and the World Health Organisation (WHO).

During the last 4 year NS Macklon has received salary/fees or grant support from the following organisations (in alphabetic order); Abbott, Anecova, ArtPRED, Clearblue, IBSA, Merck Serono, Ferring, Gedeon Richter, London Women's Clinic, Vivoplex, University of Copenhagen, Zealand University Hospital and Zealand Health Region, Denmark.

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