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NEW DEBATE

A call for more transparency of registered clinical trials on endometriosis

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In response to the pressing need for more efficacious and safer therapeutics for endometriosis, there have been numerous reports in the last decade of positive results from animal and *in vitro* studies of various compounds as potential therapeutics for endometriosis. A handful of these have undergone phase II/III clinical trials. Since the announcement of the International Committee of Medical Journal Editors that mandated registration as a prerequisite for publication, 57 endometriosis-related clinical trials have been registered at ClinicalTrials.gov, an Internet-based public depository for information on drug studies. Among them, 25 are listed as completed, and 2 as suspended. There are 15 completed phase II/III trials, which evaluated the efficacy of various promising compounds. Yet only three of the 15 trials (20%) have published their results. The remaining 12 (80%) studies so far have not published their findings. We argue that this apparent lack of transparency will actually not benefit the trial sponsors or the public, and will ultimately prove detrimental to research efforts attempting to develop more efficacious and safer therapeutics for endometriosis. Thus we call for more transparency of clinical trials on endometriosis.

Key words: clinical trial / disclosure / endometriosis / registration / transparency

Endometriosis, characterized by the ectopic presence of endometrial-like glands and stroma, is a common and debilitating gynecological condition with an enigmatic pathogenesis (Giudice and Kao, 2004). Due to the high recurrence risk post-surgery (Wheeler and Malinak, 1983; Evers *et al.*, 1995; Garry, 2004; Guo, in press), medical treatment is often needed. The current medical treatment modalities for endometriosis, however, are only somewhat effective in relieving endometriosis-associated pain, often with relatively short-term effect (Waller and Shaw, 1993). In addition, they have many undesirable, and sometimes severe, side effects (Kiilholma *et al.*, 1995; Lessey, 2000; Bulun *et al.*, 2005; Kennedy *et al.*, 2005), which may prohibit the long-term management that is needed for endometriosis. The continuous use of combined oral contraceptives, although perhaps exhibiting the best cost-effectiveness characteristics, is still far from optimal. Consequently, more efficacious therapeutics, preferably with improved safety and cost profiles are sorely needed (Nothnick and D'Hooghe, 2003; Fedele and Berlanda, 2004). In response to this need, there have been numerous reports of positive results from animal and *in vitro* studies of various compounds as potential therapeutics for endometriosis in the last decade [reviewed in (Guo, 2008)], and for a handful of them, phase II/III clinical trials have commenced.

Mandate for registration of clinical trials and the demand for publishing the results

Approximately a decade ago, most, if not all, clinical trials were shrouded with secrecy, in the name of proprietary or privileged rights. The public was kept in complete darkness, totally unaware of their existence, let alone of any significant adverse effects of a trialed compound. Believing that this situation was not in the best interests of the American people, the US Congress decided to encourage openness by enacting Section 113 of the Food and Drug Administration Modernization Act (FDAMA 113) in November 1997.

Section 113 ultimately led to the creation of ClinicalTrials.gov as an Internet-based public depository for information on studies of drugs, including biological compounds, that are conducted under the FDA's investigational-new-drug regulations (Drazen and Wood, 2005). In September 2004, the International Committee of Medical Journal Editors (ICMJE) announced that its journals would not publish the results of any clinical trial that had not been appropriately registered at ClinicalTrials.gov or another qualified public registry by 13 September 2005 (De Angelis *et al*., 2004). This journal, *Human Reproduction*, also enforced this rule. The ICMJE announcement prompted a surge of registrations at ClinicalTrials.gov, especially from industry (Zarin *et al*., 2005). Clinical trials investigating new treatments for endometriosis were no exception (Guo and Olive, 2007).

Echoing these requirements for more openness, the World Health Organization also launched, in May 2007, a new web site that enables researchers, health practitioners, consumers, journal editors and reporters to search more easily and quickly for information on clinical trials. On 27 September 2007, the US Congress enacted the FDA Amendments Act of 2007 (FDAAA), or Public Law 110-85. On the same day, the FDA Revitalization Act was signed into law, which aims to improve the FDA's ability to ensure the safety of the nation's drugs and medical devices. Section 801 of FDAAA mandates the expansion of ClinicalTrials.gov and provides for the first federally-funded trial results database. It also calls on the National Institutes of Health to augment ClinicalTrials.gov to include a 'basic results' database by September 2008. As specified by the law, the data elements include participant demographics and baseline characteristics, primary and secondary outcomes and statistical analyses and disclosure of agreements between sponsors and non-employees restricting researchers from disseminating results at scientific forums. A draft version of 'Basic results' data element Definitions, posted on 22 September 2008, at ClinicalTrials.gov lists 'participant flow', 'arm/group', 'milestone(s)', 'reasons not completed', 'adverse event', 'baseline characteristics', 'baseline measure(s)', 'outcome measures', 'measure type', 'measure of dispersion', 'unit of measure', 'outcome data' and 'descriptive statistics' as required data elements, and 'statistical analyses', 'comparison group selection', 'statistical test of hypothesis', '*P*-value', 'method' and 'method of estimation' as conditionally required. These data elements collectively capture the essence of a clinical trial from design to end. Generally, these data will be available to the public within 12 months of trial completion or within 30 days of FDA approval (or clearance) of a new drug, biological or device. Clearly, the pressure is mounting for more transparency of all clinical trials, to the benefit of those who research disease pathogenesis, and ultimately to those who suffer from conditions such as endometriosis.

Clinical trials on endometriosis: cause for alarm and concerns?

Searching the ClinicalTrials.gov website with the keyword, 'endometriosis', turned up 57 registered clinical trials as of 4 October 2008 (Table I). Of these, several trials are only remotely related with endometriosis, and some are actually observational in nature (Table I).

Two phase II/III trials on the use of rosiglitazone to treat endometriosis (NCT00121953 and NCT00115661) are listed as 'suspended' (www.ClinicalTrials.gov, accessed on 4 October 2008). The cited reason for suspension was 'due to the recent meta-analysis about CV [cardiovascular] adverse effects', apparently referring to findings reported in Singh *et al*. (2007) and Dahabreh (2008).

Twenty-five trials are listed as 'completed'. Among them, four are observational studies, two are phase IV studies (NCT00621179 and NCT00286351), two are phase I studies (NCT00090389 and NCT00041899) and another two (NCT00063310 and NCT00564135) are only peripherally related with endometriosis (Table I). This leaves 15 phase II/III completed clinical trials, which evaluated the efficacy of various promising compounds ranging from selective progesterone receptor modulators, selective estrogen receptor (ER) modulators (including an ERβ agonist), anti-tumor necrosis factor (TNF) monoclonal antibody, GnRH antagonists, aromatase inhibitors, immunomodulators (pentoxifylline), traditional medicine and two cryptically coded proprietary compounds. Among these 15 trials, 3 (20%) have published their results, but the remaining 12 (80%) studies so far have not published their findings, even though some of these trials were completed as long as seven years ago (Table I).

None of the three published clinical trials reported promising results. The phase II clinical trial (NCT00604864) on the use of infliximab, an anti-TNF monoclonal antibody, to treat deep endometriosis (a rectovaginal nodule of $\geq$1 cm) found no difference in any of the outcome measures between the treatment and control groups (Koninckx *et al*., 2008). Another trial (NCT00632697) involving 104 patients found that post-operative pentoxifylline treatment (800 mg/day) immediately after laparoscopy achieved a higher increase in cumulative probability of pregnancy within 6 months after surgery as compared with those receiving placebo post-operatively, but the difference failed to reach statistical significance (14%, 95% confidence interval: 2–30%) (Creus *et al*., 2008). The phase II clinical trial on raloxifene (NCT00001848) found that raloxifene treatment is associated, unexpectedly, with earlier return of pain symptoms as compared with placebo. For this reason, the study's Data Safety Monitoring Committee decided to terminate the study early (Stratton *et al*., 2008). These studies, in a published and publicly accessible form, contributed to our knowledge base on endometriosis therapy and prevented future patients from being exposed to ineffective or inferior treatment options.

For these three published studies, of course, it is unclear as to whether the reported negative findings are due to a genuine lack of efficacy, a lack of statistical power or simply the wrong patient population being investigated. For example, the infliximab study had only 7 and 13 patients in the placebo and the treatment groups, respectively, and the study may have been underpowered to detect a small yet clinically meaningful difference. In addition, the study recruited patients with deep endometriosis-associated pain, instead of women with active peritoneal inflammatory endometriosis as in the three baboon studies that showed promising effects of TNFα blockers (D'Antonio *et al*., 2000; D'Hooghe *et al*., 2006; Falconer *et al*., 2008); this difference could account for the discrepancy between animal and human studies. Regardless, these studies have provided sufficient details to document possible uncertainties, which will be helpful in designing future studies. Of the 12 completed clinical trials for which no information on their outcomes is available in the public domain, 11 (92%) were sponsored by pharmaceutical companies. This appears to be a déjà vu for the clinical trial on fulvestrant

Table I Clinical trials registered at ClinicalTrials.gov when searched with the keyword, endometriosis (accessed on 4 October 2008)

Identifier	Sponsor	Name of the trial	Type	Phase	Status (date of completion)	Outcome	Pubmed searched
NCT00464139	University Hospital, Gasthuisberg	Prevalence of Endometriosis in a Well Defined Group of Infertile Women	O	NA	C 2/2007	Published (Meuleman *et al.*, 2008)	Y
NCT00462176	University Hospital, Gasthuisberg	Laparoscopic Segmental Bowel Resection for Deep Infiltrating Colorectal Endometriosis	O	NA	C 2/2008	Unknown	Y
NCT00461838	University Hospital, Gasthuisberg	Outcome After Multidisciplinary CO_2 Laser Laparoscopic Excision of Deep Infiltrating Colorectal Endometriosis	O	NA	C 7/2004	Unknown	Y
NCT00194233	University of Pennsylvania	Serum and Peritoneal Fluid Bank for Endometriosis Markers	O	NA	C 6/2008	UNK	Y
NCT00001848	National Institutes of Health Clinical Center (CC)	The Safety and Effectiveness of Surgery With or Without Raloxifene for the Treatment of Pelvic Pain Caused by Endometriosis	I	II	C 1/2006	Published (Stratton *et al.*, 2008) ND	Y
NCT00604864	Katholieke Universiteit Leuven	Effect of Anti-TNFa Upon Deep Endometriosis-Associated Pain (Infliximab)	I	II	C 11/2005	Published (Koninckx *et al.*, 2008) ND	Y
NCT00632697	Hospital Clinic of Barcelona	Pentoxifylline and Endometriosis (LETS1)	I	III	C NLT 3/2008	Published (Creus *et al.*, 2008) ND	Y
NCT00121953	National Institute of Child Health and Human Development (NICHD)	Effect of Rosiglitazone on Peritoneal Cytokines in Women With Endometriosis	I	II/III	S NLT 6/2007	UNK	Y
NCT00115661	NICHD Berlex Foundation	Use of Rosiglitazone in the Treatment of Endometriosis	I	II	S	UNK	Y
NCT00109512	Neurocrine Biosciences	Endometriosis Trial: Study of NBI-56418 in Endometriosis	I	II	C 06/2006	UNK	Y
NCT00240942	Novartis	Letrozole in the Treatment of Severe and Recurrent Endometriosis	I	II	C NLT 07/2007	UNK	Y
NCT00117481	Duramed Research	Evaluation of DR-2001 for the Management of Endometriosis-Related Pelvic Pain	I	II	C 12/2007	UNK	Y
NCT00185341	Bayer	Study to Investigate the Efficacy of a Non-Hormonal Drug Against Endometriosis-Associated Pelvic Pain	I	II	C 02/2007	UNK	Y
NCT00034047	National Center for Complementary and Alternative Medicine (NCCAM)	Endometriosis: Traditional Medicine Versus Hormone Therapy Procedure: Acupuncture Drug: Chinese Products Drug: Nafarelin	I	I/II	C 08/2006	UNK	Y
NCT00090389	NCCAM	Acupuncture for Women's Health Conditions	I	I	C NLT 5/2007	UNK	Y
NCT00244452	Solvay Pharmaceuticals	A Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Investigate the Efficacy, Safety and Duration of Effect of a Single Administration of Various Doses of Cetrorelix SR in Subjects With Histologically Confirmed Endometriosis	I	II	C 09/2006	UNK	Y
NCT00318500	Wyeth	Study Evaluating the Safety and Efficacy of ERB-041 on Reduction of Symptoms Associated With Endometriosis in Reproductive-Aged Women	I	II	C 12/2006	UNK	Y
NCT00110487	Wyeth	Study Evaluating ERB-041 in Endometriosis in Reproductive-Age Women	I	II	C 12/2006	UNK	Y

Continued

Table I *Continued*

Identifier	Sponsor	Name of the trial	Type	Phase	Status (date of completion)	Outcome	Pubmed searched
NCT00621179	Colorado Center for Reproductive Medicine	Endometrial Markers and Response of Endometriosis Patients to Prolonged GnRH Agonist Prior to IVF (Integrin IVF)	I	IV	C 02/2008	UNK	Y
NCT00160433	Abbott Jenapharm GmbH & Co. KG	A Study to Evaluate the Safety and Effectiveness of Asoprisnil in the Treatment of Women With Endometriosis	I	II	C NLT 5/2008	UNK	Y
NCT00160420	Abbott	A Long-Term Study to Evaluate the Safety of Asoprisnil in the Treatment of Women With Endometriosis From Study M01-398	I	II	C 7/2004	UNK	Y
NCT00160446	Abbott	A Study to Evaluate the Safety and Effectiveness of Three Asoprisnil Doses in the Treatment of Women With Endometriosis	I	II	C 07/2001	UNK	Y
NCT00225186	Bayer	Safety and Efficacy of SH T00660AA in Treatment of Endometriosis	I	III	C 3/2008	UNK	Y
NCT00286351	Rigshospitalet, Denmark	Use of Arimidex and Zoladex as Pretreatment to IVF in Women With Ovarian Endometriosis	I	IV	C NLT 4/2007	UNK	Y
NCT00063310	Voyager Pharmaceutical Corporation	ALADDIN Study: Antigonadotrophin-Leuprolide in Alzheimer's Disease Drug Investigation	I	II	C NLT 2/2006	UNK	Y
NCT00041899	NICHD	Comparison of Blood Levels of Two Formulations of the Selective Hormone Receptor Modulator CDB-2914	I	I	C NLT 03/2008	UNK	Y
NCT00564135	Chang Gung Memorial Hospital	Post-operative Urinary Retention and Urinary Track Infection (UTI) After Laparoscopic Assisted Vaginal Hysterectomy (LAVH) for Benign Disease	I	?	C 07/2008	UNK	Y
NCT00675779	Poznan University of Medical Sciences University of California, Davis Biomet Polska Sp. z.o.o.	Efficacy Study of Atorvastatin in Pelvic Pain Relief in Women With Endometriosis (EndoStatin)	I	?	A/NR	NA	
NCT00619866	Neurocrine Biosciences	An Efficacy and Safety Study of NBI-56418 in Endometriosis (Lilac Petal)	I	II	A/NR	NA	
NCT00437658	Neurocrine Biosciences	Safety and Efficacy Study of NBI-56418 in Endometriosis (PETAL)	I	II	A/NR	NA	
NCT00225199	Bayer	Efficacy and Safety of SH T00660AA in Treatment of Endometriosis	I	II	A/NR	NA	
NCT00173212	National Taiwan University Hospital	Proliferation of Endometrial Stromal Cells in Adenomyosis	O	NA	A/NR	NA	
NCT00212342	Nobelpharma	Efficacy and Safety Study of Low Dose Oral Contraceptive Pill to Treat Dysmenorrhea	I	III	A/NR	NA	
NCT00212277	Nobelpharma	Efficacy and Safety, Long-Term Study of Low-Dose Oral Contraceptive Pill to Treat Dysmenorrhea	I	III	A/NR	NA	
NCT00290251	NICHD	Treatment of Uterine Fibroids With the Selective Progesterone Receptor Modulator CDB-2914	I	II	A/NR	NA	
NCT00758953	KV Pharmaceutical Company	Pain Associated With Endometriosis	I	II	A/NR	NA	
NCT00073801	NICHD	Pelvic Pain in Women With Endometriosis	O	NA	R	NA	
NCT00654524	Zhejiang University	Randomized Study of Gonadotrophin-Releasing-Hormone Agonist (GnRH-a) or Expectant Management for Endometriosis	I	IV	R	NA	
NCT00458458	NICHD, NIH, State University of New York - Downstate Medical Center	Treatment of Endometriosis With Norethindrone Acetate (NA) Versus Gonadotrophin-Releasing Hormone (GnRH) Agonist (Lupron Depot 11.25 mg)	I	III	R	NA	
NCT00229996	NICHD	Medical Treatment of Endometriosis-Associated Pelvic Pain	I	III	R	NA	

NCT00119925	Radboud University ZonMw: The Netherlands Organisation for Health Research and Development	'SPRING'-Study: 'Subfertility Guidelines: Patient Related Implementation in the Netherlands Among Gynaecologists'	I	?	R	NA
NCT00556075	Repros Therapeutics Inc	Safety and Efficacy Study to Evaluate Proellex in the Treatment of Premenopausal Women With Symptomatic Endometriosis	I	II	R	NA
NCT00487409	University Hospitals of Cleveland Tyco Healthcare Group	Random Comparison of LigaSure and Disposable Staples for Laparoscopic Surgery	I	?	R	NA
NCT00625950	Instituto Valenciano de Infertilidad, Spain	Endometriosis Patients Undergoing Quinagolide Treatment	I	IV	R	NA
NCT00463398	University Hospital, Gasthuisberg	Fertility Surgery, Prospective Analysis	O	NA	R	NA
NCT00172588	National Taiwan University Hospital	Evaluation of Endometrial Stromal Cell Apoptosis in Adenomyosis	O	NA	R	NA
NCT00155051	National Taiwan University Hospital	Progestin Treatment for Endometrial Stromal Cells in Adenomyosis	O	NA	R	NA
NCT00155870	National Taiwan University Hospital	Health-Related QoL Among Women Receiving Hysterectomy in NTUH	O	NA	R	NA
NCT00354471	University of Manitoba	Uterine Artery Embolization for Symptomatic Fibroids	I	III	R	NA
NCT00757952	Pine Street Foundation	Exhaled Breath Biomarkers in Finding Ovarian Epithelial Cancer in Patients With Newly Diagnosed Ovarian Epithelial Cancer, Polycystic Ovarian Syndrome or Endometriosis and in Healthy Participants	I	?	R	NA
NCT00474851	Children's Hospital Boston Brigham and Women's Hospital	The Effect of Hormonal Add-Back Therapy in Adolescents Treated With a GnRH Agonist for Endometriosis: A Randomized Trial	I	II	NYR	NA
NCT00455845	Mahidol University	The Effectiveness of Lng IUD for Treatment of the Patient Undergone Conservative Surgery for Pelvic Endometriosis	I	III	NYR	NA
NCT00735852	Sheffield Teaching Hospitals NHS Foundation Trust Ipsen	Decapeptyl SR With Livial Add Back Therapy in the Management of Chronic Cyclical Pelvic Pain in Premenopausal Women	I	IV	NYR	NA
NCT00173407	National Taiwan University Hospital	PTEN and IGFBP-3 Correlation in Ovarian Carcinoma Invasion	I	?	NYR	NA
NCT00370123	Sheba Medical Center	The Immune Base of Endometriosis	O	NA	NYR	NA
NCT00291278	NICHD	Effects of Endometriosis on Bone Mineral Density	O	NA	NYR	NA
NCT00761683	AstraZeneca	Non-Interventional Study to Evaluate Effect of Zoladex in EndometrioSIS (ESIS)	O	NA	NYR	

O, observational; I, interventional; ND, no difference from the control group; UNK, unknown; NA, not applicable; C, completed; S, suspended; R, currently recruiting; NYR, Not yet recruiting; A/NR, active but not recruiting; NLT, no later than (usually indicates the date of 'last updated', not the completion date).

(Faslodex) which was launched in 1999 yet has remained unreported ever since (Johnston, 2002; Guo and Olive, 2007) and joined the ranks of clinical trials falling victim to publication bias. Without any detail it is difficult to know precisely whether these 12 trials were successful, but it should be remembered that the intent of registration at ClinicalTrials.gov is to benefit future research and understanding. Indeed, there is no such official requirement for registration if the results are merely intended for internal use only. Because of the huge financial investment needed for phase II/III trials, it is sensible and reasonable to expect that, should the results of the trial be positive, with desirable efficacy and safety profiles, most pharmaceutical companies that sponsored the trial would naturally jump at the opportunity to announce their findings publicly or, at least, to issue some forward-looking statements in the company's annual reports. Therefore, the lack of any public information on the fate of these clinical trials may be more likely to signal some problems in efficacy, safety or both. At the very least, one message can be gleaned from the 3 published and the remaining 12 unreported studies: there is no blockbuster drug for endometriosis yet.

What did these completed trials tell us?

Safety issues are addressed in phase I trials. Phase II and—especially—phase III trials address effectiveness as well. The negative results reported (and likely negative results not reported) by the 15 registered phase II/III trials present a stark contrast to the nearly overwhelming and exciting preclinical findings. Assuming, perhaps not unreasonably, that this rather unusual silence is a telltale sign of somewhat unexpectedly high risk/benefit ratios uncovered in these trials, we can see that the development of novel and efficacious therapeutics to treat endometriosis-associated symptoms, especially pain, may be more challenging than was originally realized. However, the information asymmetry, or lack of transparency, in these trials prevents us from understanding what went wrong, and our ability to learn from these studies is limited.

Failure is the mother of success

Roughly half of candidate compounds entered into phase II/III trials eventually fail. Hence failure is part of the normal drug development process and certainly is not a stigma in the eyes of the public. In fact, unsuccessful clinical trials, if fully disclosed and adequately dissected, can teach researchers sometimes a great deal more than successfully completed trials. As Petroski so eloquently stated, 'Things that succeed teach us little beyond the fact that they have been successful; things that fail provide incontrovertible evidence that the limits of design have been exceeded. Emulating success risks failure; studying failure increases our chances of success. The simple principle that is seldom explicitly stated is that the most successful designs are based on the best and most complete assumptions about failure' (Petroski, 2006). These comments apply to the design and execution of clinical trials. Obviously, the first step in studying failure is to pinpoint its precise cause(s), even though these may not always be easy to discern, especially when information is scarce, or simply unavailable. Indeed, unlike large civil engineering projects such as dams 'whose scale is so large, whose cost is so great and whose design is so specific to the site that the structure is unique' (Petroski, 2006), a great deal can be learned from unsuccessful clinical trials since there are many commonalities in design goals and execution of clinical trials, also for those studying the treatment of endometriosis.

More transparency benefits all

The apparent gulf between the number of clinical trials conducted and the number for which results were made public was noted over 20 years ago (Simes, 1986) and is well documented (Easterbrook *et al.*, 1991; Zarin and Tse, 2008). This lack of transparency may result from, among other causes, an inherent bias against publishing negative studies by the authors, reviewers and/or journal editors, but also from the deliberate intention to conceal 'inconvenient' results (Johnson and Dickersin, 2007) possibly deemed to be embarrassing or financially damaging. A recent review of 74 FDA-registered antidepressant studies found that 31% of them were not published; the decision as to whether and how the studies were published appeared to be associated with the study outcome (Turner *et al.*, 2008). By way of comparison, in endometriosis trials the proportion of unpublished studies is much higher (80% versus 31%). Although the lack of public disclosure of results from clinical trials is not uniquely confined to endometriosis, its negative impact on endometriosis research may be disproportionately high, since fewer trials are conducted for this disease as compared with other less prevalent but more serious diseases, or common chronic disorders like Crohn's disease or rheumatoid arthritis.

For a given approved drug in wide use, this publication bias in favor of positive findings artificially inflates the estimate of a drug's efficacy, thus distorting the true risk-benefit ratio. For several clinical trials assessing the efficacy of different compounds, as in endometriosis trials, the publication bias may also be present. While this may not necessarily result in inflated estimates of drug efficacy, it certainly leaves researchers outside of the circle in the dark, hindering, intentionally or otherwise, the pace to find the blockbuster drug for endometriosis that everyone is looking for.

While the sponsors of clinical trials may claim that the disclosure of their trials might give their competitors an unfair advantage, they seem to forget a key fact: the very purpose for the mandatory registration is to make clinical trials of new treatment public knowledge, including the good (efficacy) and the bad (lack of efficacy, and/or adverse events) results. When everybody is holding their cards close to their chests, nobody will benefit from hard-earned lessons and everybody will be condemned to repeat others' mistakes and miscalculations. When clinical trial data are cloaked under proprietary secrecy, no 'unauthorized' scientists are able to scrutinize the data to draw what could be critical insight. Unless sponsors themselves are completely equipped and fully competent to scrutinize the data, some invaluable insight would be forever lost, along with their investment, to the detriment of the cause to uncover better therapeutics for endometriosis and other conditions.

Above all, this approach appears to put a higher value on economics and perceived self-interest than on those brave and altruistic trial participants who have placed themselves purposefully at risk by volunteering for clinical trials in the hope that a better treatment for endometriosis might be discovered. These participants 'deserve to

know that the information that accrues from their altruism is part of the public record, where it is available to guide decisions about patient care, and deserve to know that decisions about their care rest on all of the evidence, not just the trials that authors decided to report, that reviewers decided to accept and that journal editors decided to publish' (De Angelis *et al*., 2004). It has been argued that when patients, motivated by altruism, participate (or even consider participating) in a clinical trial, they are entitled to understand fully all the options available to them in the various trials that are currently recruiting subjects. In addition, their participation in a clinical trial should result in generalizable knowledge that will be available to future patients and investigators to improve patient care. This can happen only when appropriate details of the clinical trial are made available to the public in a timely fashion (Drazen and Wood, 2005). More transparency is thus in line with these arguments. Not publishing negative result studies is unethical.

A call for more transparency of endometriosis clinical trials

With reported endometriosis prevalence in the range of 1–22% in women of reproductive age and ~50% of women with infertility (Mahmood and Templeton, 1991; Olive and Schwartz, 1993), the worldwide collective health care cost of endometriosis is massive (Simoens *et al*., 2007). Yet since it is not a fatal disease and only affects women, research involving endometriosis appears to be underfunded, especially when compared with trials of, for example, drugs for cardiovascular diseases, which have been funded and conducted long after their effectiveness had been proven beyond any reasonable doubt in clinical megatrials. The lack of transparency of endometriosis trials only makes this situation worse and inevitably forces researchers to repeat previous errors and expose ever more patients to experimental drugs that already have been proven ineffective or even harmful; this could be avoided if there would be more transparency.

The apparent gap between the generally promising preclinical findings and the unimpressive clinical trial outcomes in endometriosis reflects, presumably, our current woefully inadequate understanding of the mechanisms underlying endometriosis-associated pain and subfertility. It highlights the difficulty in developing new therapeutics for endometriosis, and calls for more research into the etiology and pathogenesis of endometriosis. Indeed, non-surgical treatment of endometriosis may be arguably more challenging than treating cancers, since patients with endometriosis, essentially a non-fatal disease, may be less tolerant of pharmaceutical side-effects. In addition, the relationship between severity of endometriosis and of symptoms such as dysmenorrhea is far from specific (Vercellini *et al*., 2006; Liu and Guo, 2008). The finding from the raloxifene trial that the recurrence of histologically proven endometriotic lesions did not correlate with the recurrence of pain symptoms (Stratton *et al*., 2008) is a rude reminder. In our opinion, more transparency of registered clinical trials on the treatment of endometriosis, especially the disclosure of results of clinical trials within a reasonable timeframe, will actually benefit, rather than hurt, all sponsors of clinical trials. With a better understanding of what can go wrong, what does not work and what could work, and why, we should have a better chance of developing more efficacious and safer therapeutics for endometriosis, and ultimately better serve women with the condition. Indeed, by instituting a policy or mandate for disclosure, disclosing the trial results would be less likely to be viewed by its sponsor as a 'zero-sum game'. As a result, all competitors can compete on a higher level, with a subsequent improved likelihood of bringing better products to the market. In conclusion, we call upon all sponsors of endometriosis clinical trials, both investigator initiated as well as industry sponsored, to openly and voluntarily disclose their trial results within a reasonable timeframe (within which data collection, analyses and dissemination can be done adequately). Specifically, we call upon all investigators to disclose their trial data to the public within 12 months of trial completion. In our opinion, this would be the only correct thing to do, morally, ethically, scientifically and no doubt economically, if we are ever to crack the enigma that currently is endometriosis.

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