

LUPRON VICTIMS HUB

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OPEN RESPONSE to The WHO Statement on Public Disclosure of Clinical Trial Results

The WHO's attempt via its Draft Statement to ensure transparency in the reporting of all clinical trial results is commendable and most welcome. But this effort absolutely must extend to include transparency for **ALL PAST** clinical trial data as well, and not just a prospective data collection effort. In addition, enforceable mechanisms **MUST** be devised and implemented to prevent alteration and/or fabrication of data at the primary dataset entry points. A few concrete, and disturbing, examples of fraudulent clinical trial data and the ease of alteration in and to computerized records will be provided, and should best illustrate these needs.

In 1997, long after I had contacted the manufacturer and FDA in efforts to learn the incidence of adverse events reported for the drug "Lupron" (leuprolide, leuprorelin), I wrote to WHO; and WHO responded "Leuprorelin is widely available and we have no information concerning any restrictive action relating to this product. I would suggest that you contact the FDA or the manufacturer for further information." ¹ (If WHO were to enact a retrospective Registry, I wonder what WHO's response to this query would be.)

Given what I have since learned (though **not** from the FDA or manufacturer), and as a very concerned consumer and as Founder of 'Lupron Victims Hub', I would like to address several missing – yet very critical – components of WHO's Draft Statement on Public Disclosure of Clinical Trial Results.

Line 25 of WHO's Draft Statement states: "There is an ethical imperative to report the results of all clinical trials." The WHO should address and require that this ethical imperative be expanded to acknowledge and state: "There is an ethical imperative to report - **and to independently validate** - the results of all clinical trials." Likewise, Line 61-62 of WHO's Draft Statement should read: "The benefit of sharing research data and the facilitation of research through greater access to – **and independent validation of** – primary datasets is a principle which WHO sees as important." Line 62-63 states "This statement is not directed towards sharing of primary data." I do understand the role which proprietary status plays, but it is this primary data that is precisely at issue, and this is the data that needs corroboration and authentication.

The raw, primary, unpublished (endometriosis) clinical trial data of Lupron 3.75 mg., which remain hidden under a U.S. court seal, are a *prima facie* case in point. "Results" of Lupron's 1980's endometriosis clinical trials have been "widely published", thereby giving the erroneous and hazardous

¹ Scroll to "LETTERS" @ <http://www.lupronvictimshub.com/documents&correspondences.html>, see "12-18-97"

impression that these trials' data and outcomes have been openly disclosed. One outcome, as asserted by the manufacturer in Lupron's label, is that the Lupron-induced ovarian suppression is "reversible upon discontinuation of therapy"². However, during a 2011 Lupron product liability trial, the plaintiff's medical expert accessed the thousands of pages of Lupron's court-sealed, raw, unpublished data - and this 2011 analysis found (among other findings) that "62.5% of patients had not regained baseline estrogen levels by one year after stopping Lupron", which identified "definitive evidence of long-term damage to ovarian function."³ This very significant and most alarming adverse outcome is **not published** in any medical journal, was **not provided** by the manufacturer to the FDA prior (or subsequent) to Lupron's 1990 FDA approval for pain management of endometriosis, and this serious iatrogenic adverse outcome **remains unknown** to physicians and consumers to this day.

While the WHO's focus is upon the registration and publication of all prospective interventional trials, the gross discrepancy between the above-mentioned claimed and published Lupron 3.75 mg's effects ("reversible upon discontinuation") and the independent raw data analysis ('62.5% failed to return to baseline estrogen levels one year after stopping Lupron') illustrates the fact that "**publication of results**" **does not prevent or prohibit in any way the promulgation of fraudulent data and hence fraudulent outcomes**. This independent analysis of Lupron's raw data should indicate, and support, the need for public disclosure of **retrospective data** as well as prospective trials. (Please take note that when the FDA was informed in 2011 that independent analysis of Lupron's 1980's raw clinical trial data revealed *data which did not support* the manufacturer's claimed outcome, the FDA deemed no action was necessary – and failed to acknowledge or address the issue of Lupron's concealed data and fraudulent outcomes.⁴)

Other striking and noteworthy clinical trial data 'anomalies' involving Lupron that are worthy of mention can be found in the published results of clinical trials conducted to gain the initial 1985 FDA approval of Lupron - for palliative treatment of prostate cancer. "Results" of data from these studies^{5, 6, 7} revealed (and promoted the fact that) Lupron had 'insignificant cardiac adverse events'⁸. (Subsequently, Lupron became *the most prescribed* GnRH analog). However, decades later, a large study would show that the use of Lupron (and other GnRH analogs) for androgen deprivation therapy in management of prostate cancer was associated with a "10 – 50% increase" in the risks of coronary heart disease, myocardial infarction and sudden death⁹; and in 2010 the FDA issued an alert and label change warning of Lupron/GnRH analogs' risk of heart attack, sudden cardiac death, and stroke¹⁰.

² http://www.rxabbvie.com/pdf/lupron3_75mg.pdf

³ http://www.lupronvictimshub.com/lawsuits/Klein_Amicus_Published.pdf - see page 13 of *amicus curiae* brief (a.k.a. page 26 of document).

⁴ http://www.lupronvictimshub.com/lawsuits/FDA_Redwine_2013.PDF

⁵ 'Leuprolide versus Diethylstilbestrol for metastatic prostate cancer- The Leuprolide Study Group', NEJM, 311(20):1281-6. November 15, 1984. <http://www.nejm.org/doi/full/10.1056/NEJM198411153112004>

⁶ 'Luteinizing Hormone-Releasing Hormone Analogs in Treatment of Prostate Cancer'; Smith, JA. Urology (Supplement), 27(1):9-13. January 1986. (98 subjects received Lupron).

⁷ 'Leuprolide versus Diethylstilbestrol for previously untreated stage D2 prostate cancer'. Garnick, MB. Urology (Supplement), 27(1):21-6. January 1986. (98 subjects received Lupron).

⁸ For further details on cardiac adverse events provided to and withheld from FDA by the manufacturer prior to Lupron's 1985 approval, see page 4 @ <http://www.lupronvictimshub.com//home/USAdraft.doc>

⁹ 'Survival Following Primary Androgen Deprivation Therapy among Men with Localized Prostate Cancer', Lu-Yao GL, et al. JAMA, July 9, 2008; 300(2):173-81. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2645653/>

¹⁰ <http://www.fda.gov/Drugs/DrugSafety/ucm229986.htm>

Moreover, “results” of the data from Lupron’s 1980’s prostate cancer clinical trials (i.e. Study M81-107), as published in the journal Urology, reported “2 out of 98 subjects”¹¹ as having experienced the adverse reaction of impotence (while an FDA review of this study found “4 subjects”¹²) - yet it is now widely known and accepted that Lupron/GnRH analogs cause a near-universal impotence and loss of sex drive. In a small 1999 study evaluating the effect of leuprolide on prostate cancer patients, it was found that leuprolide “strongly suppresses erectile function and sexual activity”, and “sexual desire, sexual interest and sexual intercourse were totally annulled.”¹³ Other large scale studies have revealed “80% of those on [Lupron/GnRH analogs] reported being impotent”¹⁴ and “a 267% increase in impotence was observed after one year of treatment”¹⁵. In fact, due to this now-admitted and expected universal adverse sexual effect, Lupron is promoted and used as chemical castration in sex offenders^{16, 17, 18, 19, 20}. How is it that Lupron’s researchers and manufacturer ‘arrived’ at the ‘disclosure’ in their published study results that only 2 (out of 98) subjects experienced the adverse reaction of impotence, while today’s impotence rates for men on Lupron/GnRH analogs are understood to hover around 100%?

The WHO should create and require a mechanism that can provide **independent validation** of the alleged data that is ‘reported’ by researchers and pharmaceutical companies. And the WHO should recognize that presently **there is NO mechanism** to prevent a researcher and pharmaceutical company from fabricating data – and even subjects – out of thin air. Again using Lupron as an example, it became known only as a result of a whistleblowing nurse’s integrity and courage that several **peer-reviewed and published** Lupron “studies”²¹ contained, in fact, totally fabricated data **and** fabricated subjects.²²

Also, very alarmingly, in the course of the 2001 U.S. Department of Justice’s investigation of Lupron’s then-manufacturer’s (Takeda Abbott Pharmaceuticals [TAP]) conspiracy with physicians to bill insurers for free Lupron samples, it was revealed that a **computer program** was given by TAP to many doctors in the country (some 10,000 urologists were offered gifts from TAP²³), and this program would compute

¹¹ *Supra*, 7; at page 25

¹² NDA 19-010. Lupron (leuprolide acetate) Summary Basis of Approval. ‘Statistical Review & Evaluation’, April 13, 1985. (89 evaluable subjects)

¹³ ‘Erectile function and nocturnal penile tumescence in patients with prostate cancer undergoing luteinizing hormone-releasing hormone agonist therapy.’ Marumo K., et al. International Journal of Urology, 6(1):19-23. Jan 1999. <http://www.ncbi.nlm.nih.gov/pubmed/10221860>

¹⁴ ‘Quality of life following localized prostate cancer treated initially with androgen deprivation therapy or no therapy’. Potosky AL, et al. JNCI, 94(6):407-9. March 20, 2000. <http://www.ncbi.nlm.nih.gov/pubmed/11904315>

¹⁵ *Supra*, 9

¹⁶ ‘Treatment of sex offenders with leuprorelin’ - <http://www.ncbi.nlm.nih.gov/pubmed/16505878>

¹⁷ Lupron (a.k.a. Prostag) used in UK experiment to “crush” prisoners’ sex drive - <http://www.dailymail.co.uk/news/article-2114341/One-paedophiles-chemically-castrated-controversial-prison-experiment-crush-sex-drive.html>

¹⁸ ‘Treatment of paraphilia in young adults with leuprolide acetate: a preliminary case report series’ - <http://www.ncbi.nlm.nih.gov/pubmed/15568711>

¹⁹ ‘Leuprolide acetate is a familiar drug that may modify sex-offender behavior’ - <http://www.ncbi.nlm.nih.gov/pubmed/16536753>

²⁰ ‘Pharmacotherapy of paraphilias with long-acting agonists of luteinizing hormone-releasing hormone: a systematic review’ - <http://www.ncbi.nlm.nih.gov/pubmed/12927003>

²¹ i.e., “Retracted”: <http://www.ncbi.nlm.nih.gov/pubmed/8339817>

²² Federal Register, Vol. 61, No. 85, pages 19295-6; May 1, 1996. “Notice of Scientific Misconduct”, reproduced @ http://www.lupronvictimshub.com/home/FedRegister5_1_96.doc

²³ <http://www.businessweek.com/stories/2002-06-23/a-whistle-blower-rocks-an-industry>

the amount of money per Lupron prescription the doctor could earn²⁴; this computer program also harbored a 'secret key' - in the event the computer program calculating the Lupron/patient earnings was in danger of discovery, the key could be struck and !presto! **all incriminating information disappeared**^{25, 26}.

What mechanisms does the WHO have to deal with and/or prevent similar and related scenarios? After a study of WHO online resources, it would appear that the International Clinical Trials Registry Platform (ICTRP) has identified that Primary Registries should "meet the [ethical] requirements of the ICMJE [International Committee of Medical Journal Editors]"²⁷, and the WHO's Primary Registry Criteria for "Quality and Validity" notes Primary Registries "will have a mechanism in place to ensure the validity of the registered data (ICMJE [International Committee of Medical Journal Editors])."²⁸ But **what is** this mechanism?

The ICMJE page on scientific misconduct merely states "the editor should initiate appropriate procedures detailed by such committees [] as the Committee on Publication Ethics (COPE)."²⁹ Yet COPE provides only flowcharts of what to do in the event of a questionable *submitted or published publication*³⁰, a time-frame **after** data massage. What about provisions, safeguards, oversight, etc. at the **data entry** point? It would seem to me that one should earnestly try to lock a barn door **before** the horse escapes. Why are measures developed for editors to deal with possible scientific misconduct related to alteration or fabrication of primary datasets in submitted or published manuscripts, when there should be mechanisms devised and implemented to ensure there is oversight, accuracy, and validation of the data at the data collection and entry process points. If caught by oversight (or prevented by oversight) at the data entry point, what to do with "a falsified publication" becomes moot.

Ensuring and preserving the sanctity of pure primary dataset entry cannot be overstated here, and it appears that the WHO draft statement addresses none of these critical issues. Is the WHO relying on the honesty of the researchers and manufacturers to enter negative data into the computerized registry? Consider these following examples as realistic food for thought:

Abbott, the former developer, manufacturer, and marketer of Lupron (now known as AbbVie) was being examined for potential fraud by a 2010 U.S. Senate Committee on Finance, and details from the Senate Report revealed "one Abbott official suggested that local connections or the "Philly mob" should intervene to silence Baltimore Sun columnist Jay Hancock for his coverage of the [Abbott stent] scandal, saying "someone needs to take this writer outside and kick his a**".³¹

Takeda, the former developer, manufacturer, and marketer of Lupron (and now marketer of leuprorelin as "Prostap"), has been described in a lawsuit (regarding 'Actos') as having a "corporate culture riddled

²⁴ http://www.lupronvictimshub.com/history/TAP_RTP_Memo001.pdf

²⁵ <http://www.justice.gov/archive/opa/pr/2001/October/513civ.htm>

²⁶ Information also cited in 2003 Congressional Testimony (page 23) @ www.lupronvictimshub.com/home/Millican03CongressionalTestimony.doc

²⁷ <http://who.int/ictrp/network/primary/en/>

²⁸ <http://www.icmje.org>

²⁹ <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/scientific-misconduct-expressions-of-concern-and-retraction.html>

³⁰ <http://publicationethics.org/resources/flowcharts>

³¹ http://articles.baltimoresun.com/2010-12-06/health/bs-md-senate-stent-report-20101205_1_midei-stent-abbott-laboratories

with systemic fraud and deceit with motivation to falsely report and under report”, and the vice president of the Pharmacovigilance Department informed employees “As a company, reporting adverse events is one thing, but we must make sure that the company has to be profitable first”³². In another related lawsuit, the jury heard claims that “Takeda wantonly destroyed documents and files”, leading the US District Court judge to write in her ruling “The breadth of Takeda leadership whose files have been lost, deleted, or destroyed is, in and of itself, disturbing.”³³

After reports of suicide and severe depression in woman with endometriosis treated with GnRH agonists (as reported from a Japanese survey)³⁴, and after a potential signal of suicidal reactions in women with uterine fibroids treated with GnRH agonists (as originated from a Japanese academic center)³⁵, Takeda “proposed to carry out a pharmacoepidemiological study of the risk of suicide and severe depression in patients treated with these drugs.”³⁶ But while Takeda concluded “the results of the study do not suggest any increase in the risk of depression or suicide in the different female populations”³⁷, in contrast, the European Medicines Agency’s Pharmacovigilance Working Party’s (PhVWP) 2011 summary report of this same Takeda study concluded “the study revealed an increased risk of incident depression in endometriosis [] patients treated with GnRH agonists”, and “in endometriosis patients, the use of GnRH agonists was associated with around a 50% increase in the risk of incident depression”, and “[t]he PhVWP concluded that the risk of depression and mood changes should be mentioned and warnings should be included, in a consistent manner and for all indications, in the product information of all medicinal products in the EU containing a GnRH agonist”^{38, 39} (identifying leuprorelin, buserelin, goserelin, histrelin, nafarelin and triptorelin as the GnRH agonists included in their review). As a developer, manufacturer, and marketer of Lupron/leuprorelin, with profits at stake, is it acceptable to have a self-interested party conduct safety reviews of its own product?

Given, for example, the above mentioned Takeda and Abbott history, what measures has the WHO and ICTRP developed to deal with corporate cultures who could be presumed to be devoted and determined to protect the bottom line and as such would be prone to finding ways to get around providing negative results? In the early 1990’s I was enrolled as a subject in a Doppler ultrasound study of Lupron’s effects on uterine artery blood flow; no results were ever published and I can only assume the data was unfavorable. A Registry of all clinical trials prior to the first subject enrollment will prevent this type of scenario in the future, but how is the WHO to guard against the potentially nefarious A - Z machinations to hide and deceive bad data within this new Registry’s computerized parameters?

³² <http://articles.mercola.com/sites/articles/archive/2012/06/14/dangerous-diabetes-drug-still-on-market-despite-whistleblower-efforts.aspx>

³³ http://www.lawyersandsettlements.com/articles/actos/actos-bladder-cancer-side-effects-66-19505.html?ref=newsletter_bca_2014-02-16&utm_source=newsletter_bca_2014-02-16&utm_medium=email&utm_campaign+Articles#.UwFtITiYbWM

³⁴ http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/01/WC500120115.pdf

³⁵ http://www.lupronvictimshub.com/home/GPRD_Study_of_GnRH_analogues_and_depressionsuicide_Redacted.pdf

³⁶ Ibid

³⁷ Ibid, page 3

³⁸ *Supra*, 34. Study also identifies an increased risk of suicide behavior in prostate cancer patients.

³⁹

http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Product_Information/PhVWP_Recommendations/Gonadotropin/CMDh_PhVWP_049_2012_03.pdf

In my personal Lupron “treatment”⁴⁰, I experienced first-hand a deliberate, malicious, and **successful** effort of collusion to **alter** my computerized medical records in an attempt to cover-up the negligent and atrocious treatment rendered. This computer medical record alteration consisted of both **deletion** of a specific date of care (along with its recommendations and prescriptions), and also the creation – **fabrication** – of a subsequent and totally fictitious office visit (complete with “recommendations”), and I was billed for this fictitious office visit 5 times within 44 days. The deletion of my actual office visit with all its findings, notes, and treatments had been made to disappear with a stroke of a key, and the creation of a fabricated visit with fabricated details was done just as effortlessly – and shows the ease with which “information” and “data” can be manipulated to appear and disappear within a computerized system.

Should it be assumed that the WHO and ICTRP have dedicated computer wizards employed on the Clinical Trials Project’s computer system to observe, detect, and protect against whatever deviousness can be devised by those intent on ill-will? Warnings of the nefarious use and abuse of computer technology, including alteration of computerized records, have been raised since at least 1995⁴¹, and the WHO and ICTRP should make use of the most current and sophisticated tools against any and all types of potential computerized manipulation of data within this Clinical Trials Registry.

In summary, the above should emphasize the need for consumers and the medical community to have access to raw clinical trial data not just prospectively, but also retrospectively for drugs currently in use and on the market now (i.e., Lupron). And it should be crystal clear that methods need to be devised and implemented to independently validate and verify this clinical trial data, and that this data be housed and guarded within an advanced and ultra-secure computerized framework.

It should be much more than a ‘curiosity’ to the WHO (and the world) that a reported “2%” incidence of an adverse event to Lupron is ultimately shown to be, in fact, nearly a “100%” incidence; and a previously ‘insignificant’ risk of cardiac adverse events is now acknowledged to encompass upwards of a 50% increase in risk. And it is unconscionable that for 30 years and counting women are unaware of the raw endometriosis clinical trial data revealing they stand a 62.5% chance of permanent fertility damage when prescribed Lupron. Furthermore, it is totally unacceptable – and Orwellian - that gynecologists, reproductive endocrinologists, and the medical community at large, relying upon (and assuming the veracity of) “the published trial results”, are completely *clueless* about this concealed (and court-sealed) raw endometriosis clinical trial data.

There is no adequate way to describe the despicable and deleterious indifference and inaction of the FDA in its failure to address the issue of this concealed endometriosis raw data, and in the meantime more and more young and middle-aged women become disabled post-Lupron, and are marginalized and without medicolegal advocacy. Lupron victims demand to see these court-sealed raw endometriosis trials’ data, and have sought the intervention of Congress and the Courts – to no avail. We now look to the WHO and the ICTRP for recourse. Please ensure that we can see these data! If The WHO does not attempt to acknowledge, address and rectify this travesty and corruption --- who will?

⁴⁰ See www.lupronvictimshub.com/lawsuits/SJCbrief.doc. Millican v. Harvard Community Health Plan, Boston IVF, Natalie Schultz MD, Mahmood Niaraki MD, Brian Walsh MD, Selwyn Oskowitz MD, Michael Alper MD (Suffolk County, MA. Initially filed 1992. Supreme Judicial Court, Docket No. 98-P-1472; heard 2001. Pro se. Case denied.

⁴¹ The Phil Donahue Show. “Watch Out! Private Information May Not Be Private’. **Panelists:** Senator Patrick Leahy (via satellite), Lynne Millican, Ram Avrahami, Stephen Shaw, Evan Hendricks, Connie Hetling, Daniel (a Skip Tracer). Record date December 12, 1995. . Air date August 8, 1996.

