Marketing novel devices in medicine with reference to gynaecological innovations: Ethical dimensions

Z Abdool[1], M de Roubaix[2]
[1] Department of Obstetrics and Gynaecology, Steve Biko Academic Hospital, University of Pretoria, Pretoria, South Africa
[2] Department of Philosophy, Centre for Applied Ethics, University of Stellenbosch, Stellenbosch, South Africa

Abstract
New scientific and technological discoveries in all spheres of Medicine continuously challenge the boundaries of healthcare. To this end, the discipline is considered progressive and accomplished. The birth of this heavily professionalized discipline has leveraged the potential for the healthcare industry to innovate, regulate and disseminate proprietary products with relative ease. The rise and fall of four novel gynaecological devices represent excellent examples of ethical dilemmas in clinical medicine. This paper aims to deconstruct the power versus knowledge conflict, and suggest that reappraisal and recourse to Aristotelian virtue ethics will assist in shifting the decisional power balance primarily towards the physician.

1. Introduction: Medicine, a dynamic discipline?

1.1. Evolution of medicine- a necessary endeavour

The twentieth century has witnessed advances in medicine introducing extraordinary challenges to physicians, patients and the healthcare industry (HCI). The rationale for the introduction of 'new and improved' drugs, medical devices or technology is to optimize human life qualitatively and quantitatively by improving all health-related domains.[1,2,3] Conferring benefit without harm is fundamental for the physician and improved health with reduced suffering is an important expectation of the patient. Thus, medicine is a necessary endeavour that continuously expands, challenging the boundaries of science and ethics. Simplistic devices (tongue depressors, stethoscopes) were readily incorporated in clinical medicine. The introduction of penicillin heralded a revolution in the treatment of common and serious infections. Yet medical devices such as implants, surgical instruments, and medical equipment have ignited controversy amongst the HCI, regulatory authorities, physicians and patients due to concerns of efficacy and safety. Litigation, regulatory alerts/notifications, manufacturer recalls and ultimately the banning of medical devices signify the extent of these controversies. Examples of such medical devices include metal-on-metal hip implants, pacemakers, heart pump controllers, anaesthetic delivery systems and gynaecological devices. (www.fda.gov). Innovations like the Dalkon Shield intrauterine device (IUD), laparoscopic power morcellators (PMs), transvaginal mesh (TVM) implants for pelvic organ prolapse (POP), and the Essure™ PBC (permanent birth control) system have entered the market with great initial enthusiasm, only to exit after safety concerns, litigation and eventual banning. Is this disruptive innovation? Philosophically this conundrum demonstrates the power of the HCI over both physicians and society, or an imbalance of the 'power and knowledge' relationship between the HCI, physicians and patients? In the context of deconstructing the introduction of novel devices in medicine, the words of French philosopher, Michel Foucault, ring true:

'*People know what they do; frequently know why they do what they do; but what they don't know is what they do does.*' [4]

This paper relates to gynaecological medical devices that have raised global safety concerns.

1.2. The HCI: Power to discover and deliver:

The HCI is the largest and fastest growing industry globally. The development of modern medicine in the nineteenth century set the scene for intense healthcare innovation i.e. development and application of beneficial novel devices. The success of the HCI lies in the conceptual framework of product development, followed by implementation: marketing and delivery to various stakeholders.[5] This includes physicians, the knowledgeable gatekeepers to health who are ideally positioned to disseminate innovation to society. The powerful HCI is ideally positioned to discover, develop and deliver novel products. The purpose of their marketing strategies is to align physician behaviour to desired objectives. Common strategies include:

- involvement and commercial support of medical education programs such as continuing medical education (CME)[6]
- pharmaceutical and academic 'detailing' to physicians[7]

Correspondence
Zeelha Abdool
email: Zeelha.abdool@up.ac.za

- promotion of off-label use of drugs and devices
- outsourcing clinical research to private entities such as contract research organizations (CROs)
- enticements and gift offering to physicians
- direct-to-consumer marketing

These strategies are relevant because they may influence prescribing behaviour (number of prescriptions and motivations for addition to hospital formularies) and impact on patients' health. Thus, remotely 'controlled' by the HCI, physicians are the effective ultimate purveyors of power to implement utilization objectives. How are these modes of persuasion achieved?

1.2.1. Visitation by carefully selected sale representatives ('reps') to detail products through three mechanisms: pharmaceutical detailing (aimed to educate the physician); academic detailing (physicians educate other physicians) and e-detailing (building networking platforms).

1.2.2. Involvement in CMEs and industry-sponsored research to introduce and promote novel medical devices. Academic discussions coupled with product information subtly shifts marketing to a new level. Arrays of print materials and logo embossed stationary are made available to reinforce the 'reminder effect'.

1.2.3. Shaping medical opinions via identification of key opinion leaders (KOLs) is a vital marketing strategy. KOLs are "physicians who influence their peers' medical practice, including but not limited to prescribing behaviour" (www.pharma-mkting.com/glossary/keyopinionleader). They are skilfully selected (high academic credentials; usually academically employed; experienced researchers; members of respective professional societies/organizations).[8] Ghostwriting and guest authorship are other effective strategies to shape and control research outcomes and is the core business of some companies.[9]

1.3. Does it change practice?

The majority of studies are affirmative. Both small and elaborate enticements such as free lunch, dinners, pens and free luxurious getaways have the power to influence prescription in favour of promoted products.[10,11] The acceptance of samples may be equally effective. More scripts are written in favour of the sample supplied compared to those not advertised or the preferred drug choice.[12,13,14] This practice illustrates the power of hidden bias that is introduced by accepting samples, conceptually another form of gifting. In South Africa, only gifts with low intrinsic value are permitted for distribution (www.marketingcode.co.za) while the United Kingdom General Medical Council (GMC) suggest that doctors may accept unsolicited gifts from patients after careful consideration of several potential implications such as impact on professional decision making apart from others (www.gmc-uk.org). "Gifts are a symbolic representation of power and relationships. Their moral implications lie in the innate power of the act, inevitably creating a sense of debt and pressure to appropriately reciprocate".[15,16]

Gifts represent a more direct and measureable outcome for altering prescription behaviour, meetings with 'reps', CMEs, R&D, KOLs and ghostwriting/guest authorships are more subtle ways laden with power to influence. Thus, there is a need to regulate this relationship to ensure patient safety is considered and prioritized across all platforms.

2. Novel devices in Gynaecology:

The term 'novel' is based on the Latin novellus "new, young, fresh," thus necessitating a sense of the thoroughness of testing 'novel devices' prior to human use. The last few decades witnessed the rise and fall of several gynaecological devices, including two contraceptive devices (Dalkon Shield IUD and the Essure™ (PBC) system); laparoscopic PMs and TVM for POP. These devices raised significant scientific, ethical and regulatory issues pertaining to device safety. Women suffered harm, disability and death which resulted in professional, social and regulatory discreditation of these devices. An illustrative brief synopsis of these devices follows:

The Dalkon Shield IUD: Conceptualized and invented by Gynaecologist Dr H.J. Davis in 1968, this was an attractive option against the background of alarming side effects related to oral contraceptives. Though claiming high contraceptive efficacy, the actual pregnancy rate was double that of on-market devices (Lippes loop, intrauterine Copper devices)[17]. The Dalkon Shield was a plastic device attached to a multifilament nylon string. Aggressive marketing resulted in more than four and half million IUDs distributed in eighty countries by 1975. By 1974 increasing reports of infectious morbidity and mortality raised questions about the causal relationship between this IUD and pelvic sepsis. Moreover, efficacy was also questioned and studies showed higher pregnancy rates and risk for pelvic sepsis compared to other IUDs on the market.[17] Litigation began, domestic US sales were halted and unsold product retrieved, while distribution in less-developed countries continued.[18] The company filed for bankruptcy protection in 1985. This contraceptive saga is infamous as the largest tort case in history. It also prompted the ushering of the 1976 Medical Device Amendment Act to regulate medical devices as a regulatory oversight for ensuring patient safety.[19]

The Essure™ PBC was approved by the FDA in 2002 as a permanent form of birth control conditional to a five year approval study report. This metal coil was inserted under hysteroscopic guidance into the fallopian tubes to stimulate tissue growth (fibrosis) thereby occluding tubal patency. Demonstration of tubal occlusion with a hysterosalpingogram three months later was mandatory, as was continued use of a contraceptive of choice during this time. It was marketed as a 'minimally invasive' (office) procedure, and appealing, obviating the need for general anaesthesia.[20] The FDA deemed the device reliable based on two non-randomized prospective single-arm clinical trials that lacked a comparator group. Efficacy data was limited to those women with confirmed occlusion of the fallopian tubes i.e. a skewed cohort.[21] Since 2002, thousands of adverse events have been reported by the FDA relating to safety concerns of the device, including death (www.fda.gov/MedicalDevices/). It remains unclear why the first post-approval study was published only thirteen years after the device approval process. A global recall of this device has begun and the company voluntarily decided to discontinue sales after 31st December 2018 for business reasons.

Laparoscopic PMs: Approximately 600 000 hysterectomies are performed annually in the USA and the laparoscopic approach is becoming more popular.[22] Laparoscopic approach is considered preferable for benign disease and is associated with fewer surgical complications, less blood loss and shortened hospital stay compared to abdominal procedures.[23] A laparoscopic PM is used during a laparoscopic procedure when the uterus is too large to remove via the vagina. A rotating circular blade facilitates removal of large uteri (e.g. with large uterine fibroids). In 2014 the FDA discouraged the use of this device as a result of the potential to disseminate malignant and benign tissue (occult uterine sarcomas and parasitic fibroids). The reported incidence of uterine sarcomas is 0.2%. This cancer is more aggressive than endometrial cancer and is associated with a poor prognosis.[24] This decision was prompted by significant publicity and high profile case of a doctor who developed stage four leiomyosarcoma following LPM assisted laparoscopic removal of a fibroid uterus 2013. Many manufacturers have suspended sales of PMs, and physicians halted their use because of hospital mandates and fear of litigation.[25] Dr X claimed lack of informed consent as regards this risk.

TVM for POP: The first surgical mesh for POP received FDA clearance in 2002, despite its off-label use since 1970's. At the time surgical mesh was classified as a 'class II' device and did not require premarket FDA approval. Its entry into the gynaecology was aimed

at addressing the high recurrence rate associated with POP surgery – approximately one-third.[26] Mesh kits were rigorously marketed via the 510k rule. This implied that the TVM kits demonstrated substantial equivalence to already marketed predicate devices, and thus no clinical trials were required to determine safety and efficacy. In 2008 the FDA released its first public health notification after receiving thousands of complaints related to the use of TVM for POP, followed by a safety communication 2011. Major complaints included life-altering issues such as nerve damage, chronic sinus tract formation, organ perforation, need for reoperation and permanent disability. Globally more than one hundred thousand TVM lawsuits have been filed in federal courts against manufacturers, ending in multi-billion dollar settlements. The litigious atmosphere resulted in banning TVM from the Scottish, Australian and United Kingdom markets since 2017.

In summary, the design flaws, mistakes and questionable actions related to the above devices impact on manufacturers, regulatory authorities, physicians and patients. The four gynaecological devices raised tremendous ethical and scientific controversies globally and included the following points:

- Dalkon Shield: The multifilamentous nature of the Dalkon Shield string was more prone to harbouring vaginal microorganisms than monofilament strings, with resultant morbidity and mortality. Marketing was based on a single, falsely reported efficacy study; no safety studies were performed.
- Essure™ PBC: Safety and efficacy data were based on the limited scientific evidence of a skewed cohort. There was no investigation into the delay in in providing post-approval surveillance data mandated by the original approval.
- LPMs: In view of the potentially lethal consequence of upstaging cancer, a mandatory vigilance on post-use surveillance reporting should have been instituted. This lethal complication must form part of the consent process as illustrated by the case of Dr X.
- TVM for POP: Closer analysis indicates that the 510k process was essentially meant to deal with the influx of medical device approvals and not designed to determine scientific validity. Re-classification of TVM to class III medical devices (i.e. need for safety and efficacy studies) was instated only in the aftermath.

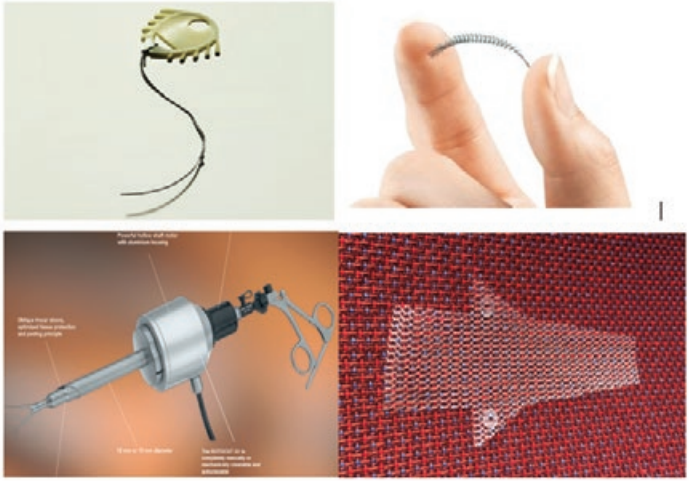

Figure 1. The Dalkon Shield intrauterine device (from http://www.professorwalter.com/2011/08/the-case-that-hung-by-a-thread.html); The EssureTM permanent birth control device (from https://www.nytimes.com/2018/07/20/health/bayer-essure-birth-control.html); A laparoscopic power morcellator used during laparoscopic removal of fibroids (www.baumhedlundlaw.com/defective-medical-device-injuries); Polypropylene mesh used to correct pelvic organ prolapse.

3. Ethical dilemma:

3.1. Nature of the ethical dilemma:

Ethical principles and moral theories have substantial value in guiding moral decision-making. An ethical dilemma requires the additional weighing up of two moral imperatives after considering the evidence.[27] Physicians have fiduciary responsibilities to patients representing a bond of trust: the former implying a standard of care that requires the physician to act in the best interests of the patient, the latter expecting that level of care.

The ethical dilemma in context derives from physicians' fundamental motivation to act in patients' best interests i.e. to provide the benefits of novel treatments while preventing harm, a classical beneficence-non-maleficence dilemma. The authenticity of the informed consent process comes into play in these situations, particularly with respect to serious but 'rare' adverse events.

Even without a formal contract, the fiduciary relationship between the parties implies that physicians wield substantial power over decisions regarding the patient. This knowledge-power-interplay also exists between the HCI, its marketing extensions, and the physician.

Scientific affirmation of medicine and development of innovative devices has resulted in a heavily 'professionalized discipline'. The use of innovative devices by clinicians has challenged the ethical principles of clinical practice. Early adopters of novel devices acquire a false sense of reassurance after regulatory approval and assume that design flaws, adverse events and long-term efficacy and safety were considered prior to approval. Innovation is aimed to benefit society; thus there is a need for all stakeholders to re-examine the introduction of novel devices to society.

5. Conclusion: Time to restore dignity:

The current reality of medicine has been reshaped and redefined by the exponential development of modern medical technological advancements. So much so, that these advances sometimes supersede our ability to fully understand the potential power of a product and therefore formulate the right questions. This represents a sharp departure from traditional medical practice and has introduced new ethical dilemmas involving marketing, profit-sharing, litigation and patient safety.

As it stands, the ultimate use of novel medical devices in the absence of robust scientific data means that current regulatory systems, guidelines and codes of practice represent insufficient control measures to guide physicians when facing new devices. The authors thus propose that the power balance be tipped in favour of the gatekeepers of medicine (i.e. physicians) to relook and reassess our notion of adopting innovation. This may be achieved, firstly by developing a stepwise pathway for medical device approval and use, with incorporation of an ethical component as outlined in figure 2.

Step one commences with the promotion of research integrity with an emphasis on abiding by the classic four principles of biomedical ethics (i.e. respect for autonomy, beneficence, non-maleficence and distributive justice).[27] Application of national regulations and international best practices such as the four principles (honesty, accountability, professionalism and stewardship) and fourteen responsibilities of the Singapore Statement are key to maintaining ethical norms.[28] This in combination with the application of virtue ethics provides a fundamental ethical platform to promote global research integrity.

In the foregoing, several questions have been raised regarding elements of informed consent. Insistence on robust safety data prior to use in patients may have eliminated conflict between beneficence and non-maleficence and allowed physicians to honour prima facie rules and obligations i.e. protecting and defending the rights of others, preventing harm from occurring to others, and removing conditions that will cause harm to others. It is impossible for physicians to meet the ethical demands of autonomy, beneficence, non-maleficence and distributive justice in the absence of robust information. In these circumstances, the four principles which represent the ethical compass of clinical practice may be insufficient to assist and guide physicians when faced with novel products. Hence, we propose a recourse to Aristotelian virtue ethics. The Greek philosopher

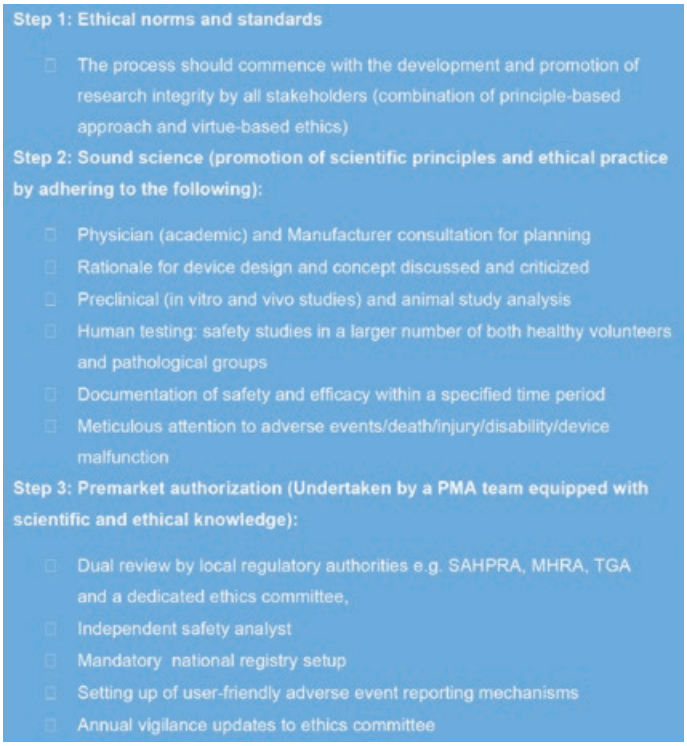

Figure 2. Proposed flow diagram for the process of new medical device evaluation and dissemination. PMA, premarket approval ; SAHPRA, South African Health Products Regulatory Authority; MHRA, The Medicines and Healthcare products Regulatory Agency; TGA, Therapeutic Goods Administration.

(384 BC- 322BC) introduced the idea that moral virtues represent the basis of an ethical life, and are learnt or acquired via practice and habit. Aristotle proposed four cardinal virtues i.e. prudence, temperance, courage and justice while Beauchamp and Childress suggest consideration of five focal virtues for healthcare professionals i.e. compassion, discernment, trustworthiness, integrity and conscientiousness, but in reality the list of applicable moral virtues is endless.[27,29] We believe that virtue ethics may assist the physician in deciding about novel treatments. Both moral (courage, truthfulness, temperance) and intellectual (intelligence, science and theoretical wisdom) virtues are value-laden and underpinned by positive attributes and that in itself is a powerful tool for physicians who conscientiously contemplate the use of novel devices.[28] In addition, country specific regulatory authorities must be coupled with academic physicians who are both scientifically and ethically focussed when considering novel device use. It is within this framework that physicians can once again become the legitimate ultimate purveyors of power.

Acknowledgements: None.
Conflict of interest: None.
Funding sources: None.

References

1. *Fuchs VR, Sox HC, Jr. Physicians' views of the relative importance of thirty medical innovations. Health Aff (Millwood). 2001;20(5):30-42. https://doi:10.1377/hlthaff.20.5.30.*
2. *Cutler DM, Long G, Berndt ER, Royer J, Fournier AA, Sasser A, et al. The value of antihypertensive drugs: A perspective on medical innovation. Health Aff (Millwood). 2007; 26(1):97-110. https://doi:10.1377/hlthaff.26.1.97.*
3. *Woolf SH, Johnson RE, Phillips RL, Jr., Philipsen M. Giving everyone the health of the educated: An examination of whether social change would save more lives than medical advances. Am J Public Health. 2007;97(4):679-683. https://doi:10.2105/ajph.2005.084848.*
4. *Foucault M, Howard R. Madness and civilization : A history of insanity in the age of reason. London: Routledge;1989.*
5. *Omachonu VK, Einspruch NG. Innovation in healthcare delivery systems: A conceptual framework. Innovation Journal. 2010;15(1):1-20.*
6. *Brody H. Hooked : Ethics, the medical profession, and the pharmaceutical industry. Lanham Maryland: Rowman & Littlefield; 2007.*
7. *Fugh-Berman A. The corporate coauthor. J Gen Intern Med. 2005;20(6):546-548. https://doi:10.1111/j.1525-1497.2005.05857.x.*
8. *Moynihan R. Key opinion leaders: Independent experts or drug representatives in disguise? Br Med J. 2008;336(7658):1402-1403. https://doi:10.1136/bmj.39575.675787.651.*
9. *Plos Medicine Editors Ghostwriting: The dirty little secret of medical publishing that just got bigger. PLoS Med.2009; 6(9):e1000156. https://doi:10.1371/journal.pmed.1000156.*
10. *Wall LL, Brown D. The high cost of free lunch. Obstet Gynecol. 2007;110(1):169-173. https://doi:10.1097/01.Aog.0000268800.46677.14.*
11. *Orlowski JP, Wateska L. The effects of pharmaceutical firm enticements on physician prescribing patterns. There's no such thing as a free lunch. Chest. 1992;102(1):270-273. https://doi:10.1378/chest.102.1.270*
12. *Adair RF, Holmgren LR. Do drug samples influence resident prescribing behavior? A randomized trial. Am J Med.2005; 118(8):881-884. https://doi:10.1016/j.amjmed.2005.02.031.*
13. *Morelli D, Koenigsberg MR. Sample medication dispensing in a residency practice. J Fam Pract. 1992;34(1):42-48.*
14. *Chew LD, O'Young TS, Hazlet TK, Bradley KA, Maynard C, Lessler DS. A physician survey of the effect of drug sample availability on physicians' behavior. J Gen Intern Med. 2000; 15(7):478-483. https://doi:10.1046/j.1525-1497.2000.08014.x.*
15. *Abdool Z. Evidence, truth, reality and power: A foucauldian analysis of the ethics of testing and using novel medical devices: Stellenbosch: Stellenbosch University; 2018.*
16. *Farah N. Gifts. Roggebaai: Kwela Books; 2001.*
17. *Sivin I. Another look at the dalkon shield: Meta-analysis underscores its problems. Contraception. 1993;48(1):1-12. https://doi:10.1016/0010-7824(93)90060-k.*
18. *Mintz M. At any cost : Corporate greed, women, and the dalkon shield. 1st ed. New York: Pantheon Books; 1985.*
19. *Wizemann TM, Institute of Medicine . Committee on the Public Health Effectiveness of the FDACP. Public health effectiveness of the fda 510(k) clearance process : Measuring postmarket performance and other select topics : Workshop report. Washington, D.C.: National Academies Press; 2011.*
20. *Kerin JF, Carignan CS, Cher D. The safety and effectiveness of a new hysteroscopic method for permanent birth control: Results of the first essure pbc clinical study. Aust N Z J Obstet Gynaecol. 2001;41(4):364-370. https://doi:10.1111/j.1479-828x.2001.tb01311.x.*
21. *Dhruva SS, Ross JS, Gariepy AM. Revisiting essure--toward safe and effective sterilization. N Engl J Med. 2015;373(15):e17. https://doi:10.1056/NEJMp1510514*
22. *Keshavarz H, Hillis SD, Kieke BA, Marchbanks PA. Hysterectomy surveillance—united states, 1994–1999. Morb Mortal Wkly Rep Surveill Summ. 2002;51(SS05):1-8.*
23. *Walsh CA, Walsh SR, Tang TY, Slack M. Total abdominal hysterectomy versus total laparoscopic hysterectomy for benign disease: A meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2009;144(1):3-7. https://doi:10.1016/j.ejogrb.2009.01.003.*
24. *Harlow BL, Weiss NS, Lofton S. The epidemiology of sarcomas of the uterus. J Natl Cancer Inst. 1986;76(3):399-402. https://doi:10.1093/jnci/76.3.399.*
25. *Mandato VD, Torricelli F, Pirillo D, Aguzzoli L, Abrate M, Palomba S, et al. Impact of the food and drug administration safety communication on the use of power morcellator in daily clinical practice: An italian survey. J Minim Invasive Gynecol. 2016;23(2):206-214. https://doi:10.1016/j.jmig.2015.09.021.*
26. *Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol. 1997;89(4):501-506. https://doi:10.1016/s0029-7844(97)00058-6*
27. *Beauchamp TL. The 'four principles' approach to health care ethics. In: Ashcroft RE, editor. Principles of health care ethics.2007.p. 3-10.*
28. *Resnik DB, Shamoo AE. The singapore statement on research integrity. Accountability in Research. 2011;18(2):71-75. https://doi:10.1080/08989621.2011.557296.*
29. *de Roubaix M. Professionalism in anaesthesiology practice: Ethical reflection on the nature of professionalism in anaesthesiology. Southern African Journal of Anaesthesia and Analgesia. 2017;23(4):79-83. https://doi:10.1080/22201181.2017.1349412*