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Invasive procedures with questionable indications

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A B S T R A C T

Insufficient coordination of medical research and partial isolation from the international scientific community can result in application of invasive methods without sufficient indications. Here is presented an overview of renal and pancreatic biopsy studies performed in the course of the operations of pancreatic blood shunting into the systemic blood flow in type 1 diabetic patients. Furthermore a surgical procedure of lung denervation as a treatment method of asthma as well as the use of bronchoscopy for research in asthmatics are discussed here. Today, the upturn in Russian economy enables acquisition of modern equipment; and medical research is on the increase. Under these circumstances, the purpose of this letter was to remind that, performing surgical or other invasive procedures, the risk-to-benefit ratio should be kept as low as possible.

Insufficient coordination of medical research and partial isolation from the international scientific community can result in application of invasive methods without sufficient indications. Here is presented an overview of renal and pancreatic biopsy studies performed in the course of the operations of pancreatic blood shunting into the systemic blood flow in type 1 diabetic patients. Furthermore a surgical procedure of lung denervation as a treatment method of asthma is discussed. The study [1] was reported as the first one to collect larger samples of pancreatic tissue from recent onset type 1 diabetic patients. Laparascopic pancreatic biopsies had been performed earlier [2]. In a series of studies from Russia, renal and pancreatic biopsies were collected during the operations of "pancreatic blood shunting into the systemic blood flow in insulin-dependent diabetics" [3] by the same researchers, who developed the concept of hypoplastic renal dysplasia [4–7]. The morphological images were partly reproduced in Ref. [8] and discussed previously [7–9]. It was concluded that the morphological images and descriptions in Refs. [4–6] could have been partly based on tangential sections of glomeruli or artifacts. It was concluded that indications to renal and pancreatic biopsies used for research in the studies [4–6,10–14] were questionable. Other studies, where biopsies were collected for research, were discussed in [9,15,16].

The same researchers collected 60 pancreatic excision biopsies 5×5 mm in size [17] during the surgical operations of "pancreatic blood shunting into the systemic blood flow in insulin-dependent diabetics." [3] From 1986 through 1994, 409 of such operations were performed in type 1 diabetic patients by this research group [3]. From the same patients, 51 renal core biopsies were collected [17]. Apart from several reports from Russia and Ukraine, [18–25] we have found in the literature no analogues of this surgical treatment modality of type 1 diabetes mellitus. The method was applied also in type 2 diabetic patients with severe hypertension [26]. The physiological mechanism, explaining for reported anti-diabetic effectiveness of the surgery, was delineated as follows: "The operation allows shunting of the venous blood flowing from the pancreas into the systemic blood flow, which should reduce the effect of glucagon on the liver, improve the correlation between injected insulin and endogenous glucagon both in the liver and in peripheral tissues." [3] The anti-diabetic effect of the above-named surgery was reported to be moderate both in humans [3,20] and in preceding experiments in dogs [27]; whereas thrombosis-related hazards [19,21], postoperative acidosis [22–24], peritoneal adhesions and other complications [24] were pointed out. Severe acidosis was stressed as a characteristic postoperative phenomenon [22], which agrees with the known fact that surgical stress can cause hyperglycemia and ketosis in diabetics [28]. It was reported that 27% of the patients developed thrombosis of the splenorenal anastomosis, confirmed by angiography, within 7–8 months after the operation [19]. In the preceding experimental study, a majority of the dogs did not survive the surgical or chemical diabetes induction and the subsequent portosystemic shunting [27], which means that the condition of surviving animals could have interfered with an objective evaluation of the anti-diabetic effect of the shunting. Morphological descriptions of pancreatic and renal biopsies in type 1 diabetes mellitus [29–31] discussed in Refs. [8,9] were partly at variance with usual morphological descriptions. [32–34]

Collection of biopsies from diabetic patients for research was planned in advance [35]. It should be noted that renal and, in particular, pancreatic biopsy is associated with risks, being considered as too hazardous a procedure for mere research purposes [1,36]. Quality of morphological examination should be taken into account determining indications to renal and pancreatic biopsies. In particular, taking of organ biopsies for scientific purposes in conditions of insufficient technical amenities and integrity is ethically

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inacceptable [15,16]. Furthermore, in the author's opinion, pancreatic blood shunting into systemic blood is not an appropriate treatment for diabetes type 1 since this surgical procedure lacks evidence of efficacy. Accordingly superfluous were the angiographic procedures [19] involving catheterization of renal and splenic veins as well as arteriography described in [3].

Another surgical procedure having no analogues in the contemporary international practice has been the lung denervation in bronchial asthma [37–42]. The procedure was applied for treatment of severe asthma with the substantiation that it (from Russian) "interrupts pathological impulses from the nervous system." [37] To achieve optimal denervation of the lung, its reimpantation (autotransplantation) for the treatment of asthma was proposed and applied in the 1960s [43]. The surgical treatment of asthma was officially approved; and recommendations by the Ministry of Health were issued and recommended for further re-editing by local health care authorities [38]. The open lung denervation via thoracotomy with "skeletonization" of the pulmonary root for severe asthma, was officially designated as the most recognized surgical method for severe asthma [38]. The lung root denervation was recommended to the patients (1) with infectious-allergic asthma having "marked blocking" of beta- adrenergic receptors; (2) severe asthma and marked glucocorticoid insufficiency; (3) after an inefficient carotid sinus denervation and glomectomy [38]. It was pointed out that duration of the medical treatment of asthma before the surgery should be reasonably limited [38]. The "closed" denervation method by means of a thoracoscope was applied as well, although the open denervation was designated as the most widely recognized procedure [38]. The carotid glomectomy was recommended for less severe conditions, such as atopic asthma with impossibility of specific desensitization [38]. In 1990, it was reported on 457 such operations performed in asthmatic patients [39]. The following absolute complication rates were reported among the 457 operated patients: postoperative complications in 58 patients, inflammatory complications in 27, bronchopulmonary (including pneumonia, empyema and pneumothorax) – in 11, neurological complications (including dysphagia and vocal fold paralysis) in 12, paraplegia or hemiparesis in 2; 6 patients reportedly died within 32 day after the operation [39]. In 2002 it was reported about continued practice of surgical lung root denervation as a treatment method of asthma resistant to medical therapy [40].

The denervation surgery was sometimes (percentages not found) accompanied by resection of pathologically altered segments of pulmonary tissue, or by lobectomy [38,41]. At the same time, the morphological images and descriptions of removed pulmonary tissue were unconvincing, having included emphysema, inflammatory and sclerotic changes without specifying their extension. Pneumonia was mentioned only as a complication of the denervation surgery [37,42]. Apart from non-specific postoperative complications, specific neurological complications of the denervation procedure were pointed out: eye dryness, palpebral oedema, hypoglossal nerve or vocal cord palsy, Horner syndrome [38]. Reported efficacy of the lung denervation procedure against asthma attacks was generally moderate, whereas approximately equal percentages (30–40%) of the patients belonged to the groups with a good, satisfactory and absent effect [41]. Objectivity of this evaluation appears questionable because no group with worsening was distinguished. Immunity- and inflammation-related indices (serum immunoglobulins, T- and B-lymphocyte content, phagocytosis-related indices etc.) were influenced by the medical and surgical treatment in the same direction, while the surgery was consistently more efficient than medical treatment [41], which appears hard to comprehend physiologically.

The use of bronchoscopy in asthma should be briefly commented. Bronchoscopy was recommended as a standard of practice for patients with severe asthma [38,44]. For example, it was reported on 756 bronchoscopies in 472 cases of asthma [44]. Although bronchoscopy with lavage and biopsy has contributed to the understanding of asthma pathogenesis, there is an opinion that these techniques have no clinical usefulness for asthmatic patients [45]. Indications for bronchoscopy in clinical practice are beyond the scope of this letter. However, bronchoscopy has been broadly used for research in asthmatics in the former Soviet Union (SU) [46–48], sometimes repeatedly [49], also in mild [50,51] and moderately severe [52,53] cases, in children [54] and the elderly [55]. At the same time, it was reported on enhanced complication rate of bronchoscopy in asthmatics, including severe complications [56]. Informed consent was mentioned only in a few recent publications [52,57]. In some studies, formalistic morphological descriptions of bronchial biopsies, significant differences of morphometric indices between patient groups e.g. with severe and moderate asthma, or uniformly increasing morphometric indices together with the duration of therapy, question, in the author's opinion, reliability and practical significance of some reported results. It should be commented that informed consent is required for experiments in humans; but another condition must be integrity. Other outdated or questionably substantiated invasive procedures used in the former SU were discussed previously [58–60].

Among the mechanisms enabling persistence of inadequate and outdated methods both in research and in clinical practice has been the authoritative management style, ingrained also in science and medicine, whereas doctors tend to follow instructions of superiors or health care authorities without questioning them on the basis of the international literature [59]. It is generally known that many former party and military functionaries, their children and relatives, occupy leading positions at universities, academies, health care authorities etc. Note that military and medical ethics are not the same. The relatively low life expectancy in Russia especially in men [61], who usually do not sit with grandchildren, is a strategic advantage: fewer pensions to be paid, etc. Many leading surgeons have been former military or originated from such families. It has sometimes strengthened the authoritative management style and impeded constructive discussion. Meshalkin and Babichev, who developed and applied the lung reimplantation [43] and denervation [41] procedures in asthmatics, had been military surgeons. Besides, the tendency towards excessive "radicalism" in surgery was partly caused by the limited availability of contemporary medical therapy e.g. for gastroduodenal ulcers [59,60]. Hyper-radicalism was known to occur also in other fields: overuse of Halsted mastectomy presented as a single treatment modality for breast cancer even in some handbooks edited as late as in 1995 [62], or routinely performed diathermocoagulation and cryotherapy of cervical pseudo-erosions (endocervical ectopia, ectropion) regardless of the presence of epithelial dysplasia; more details and references are in [59,60]. Some experts understood obsoleteness of certain locally accepted standards of practice and instructions of health care authorities, so that personal judgement was sometimes involved as well. With regard to medical ethics in Russia, it can be generalized that some of its principles, especially those concerning informed consent, have been insufficiently known and observed. Literature on medical ethics including textbooks for students tended to be vague, descriptive and hardly contained any clear instructions for actual practice-related situations. Disregard of the principle of informed consent coupled with the authoritative management style and paternalistic attitude towards patients facilitated application of surgical and other invasive methods (organ biopsies, endoscopic procedures etc.) with questionable clinical indications or for research: the patients were told that it is necessary for treatment or diagnostics, or simply not asked, e.g. in case of intra-operative biopsies. The patients' right of insight into medical records was often disregarded.

Current policies with regard to some aspects of clinical practice including ethical requirements for human experimentation in Russia are based on the National Standard for Good Clinical Practice, [63] introduced in 2006, which, as it is written in [63], is identical to the Consolidated Guidance for Good Clinical Practice issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [64]. This document was officially approved by the Federal Agency on Technical Regulation and Metrology (Rosstandart), which is certainly a step forward. At the same time, it is known that the ethical and legal basis of medical research has not been sufficiently elaborated in Russia [65]. Independent Ethics Committees started to appear in leading institutions since the late 1980s - early 1990s, while their "non-independence" and generally insignificant role were pointed out [65]. Today, the upturn in Russian economy enables acquisition of modern equipment; and medical research is on the increase. Under these circumstances, the purpose of this letter was to remind that, performing surgical or other invasive procedures, the risk-to-benefit ratio should be kept as low as possible.

Conflict of interest statement

No conflicts of interest declared.

Key learning points

- Insufficient coordination of medical research and partial isolation from the international scientific community can result in parallelism in research, unnecessary experimentation, and application of invasive methods in humans without sufficient indications;
- Performing surgical or other invasive procedures, the risk-to-benefit ratio should be kept as low as possible.

References

[1] Krogvold L, Edwin B, Buanes T, Ludvigsson J, Korsgren O, Hyöty H, et al. Pancreatic biopsy by minimal tail resection in live adult patients at the onset of type 1 diabetes: experiences from the DiViD study. Diabetologia 2014;57(4):841–3.

[2] Imagawa A, Hanafusa T, Tamura S, Moriwaki M, Itoh N, Yamamoto K, et al. Pancreatic biopsy as a procedure for detecting in situ autoimmune phenomena in type 1 diabetes: close correlation between serological markers and histological evidence of cellular autoimmunity. Diabetes 2001;50(6):1269–73.

[3] Galperin EI, Diuzheva TG, Petrovsky PF, Chevokin AYu, Dokuchayev KV, Rabinovich SE, et al. Results of pancreatic blood shunting into the systemic blood flow in insulin-dependent diabetics. HPB Surg 1996;9(4):191–7.

[4] Severgina ES, Pal'tsev MA. Hypoplastic dysplasia as one of the forms of nephropathy. Arkh Patol 1989;51(10):58–63.

[5] Varshavskii VA, Proskurneva EP, Gasanov AB, Severgina LO, Shestakova LA. Subdivision of certain morphological variants of chronic glomerulonephritis. Arkh Patol 1999;61(5):40–6.

[6] Severgina ES. Ultrastructural heterogeneity of "minimal changes" in the kidney glomeruli, detected by light optics. Arkh Patol 1991;53(2):53–8.

[7] Jargin SV. The concept of hypoplastic renal dysplasia can interfere with the diagnosis of Alport syndrome. Re: Chiricosta A, Jindal SL, Metuzals J, Koch B. Hereditary nephropathy with hematuria (Alport's syndrome). Can Med Assoc J 1970;102(4):396–401 [CMAJ response of February 14, 2014].

[8] Jargin SV. Pancreatic and renal biopsy for research: back to the indications. Molodoi Uchenyi – Young Sci 2014;(4):143–147. http://www.moluch.ru/archive/63/9770/, [accessed 08.06.14].

[9] Jargin SV. Renal biopsy for research: an overview of Russian experience. J Interdiscip Histopathol 2014;2:88–95.

[10] Severgina ES, Diuzheva TG. Morphologic and functional changers in B-cells and vessels of the islands of Langerhans in patients with insulin-dependent diabetes mellitus. Arkh Patol 1996;58(5):40–7.

[11] Severgina ES, Ponomarev AB, Diuzheva TG, Shestakova MV, Maiorova EM. Diabetic glomerulonephritis – the first stage of diabetic glomerulopathy. Arkh Patol 1994;56(4):44–50.

[12] Severgina LO, Leonova LV, Severgina ES, Gurevich AI, Menovshchikova LB, Petrukhina IuV, et al. Coupling between the hemodynamic parameters and the morphological changes in the kidney in children with congenital hydronephrosis. Arkh Patol 2011;73(2):14–7.

[13] Leonova LV, Severgina ES, Popova OP, Konovalov DM, Petruchina IuV, Simonova NA. Transforming growth factor as a marker beta of nephrogenetic disturbance in congenital obstructive uropathies. Arkh Patol 2007;69(4):35–8.

[14] Cheskis AL, Severgina ES, Leonova LV, Ostapko MS. Status and development of the kidney after surgical treatment of hydronephrosis in children. Urologiia 2002;4:39–43.

[15] Jargin SV. Chernobyl-related bladder lesions: new interpretation required. J Interdiscip Histopathol 2014;2:96–7.

[16] Jargin SV. Renal biopsy research in the former Soviet Union: prevention of a negligent custom. ISRN Nephrol 2013;2013:980859.

[17] Severgina ES. Morphology and pathogenesis of insulin-dependent diabetes mellitus. Habilitation thesis. Moscow: I.M. Sechenov Medical Academy; 1995.

[18] Siplivyi VA, Beresnev AV. The late results of deportalization of the pancreatic blood flow in patients with type-1 diabetes mellitus. Klin Khir 1998;11:9–12.

[19] Nikonenko AS, Kovalev AA, Zavgorodnii SN, Volkova NA. Surgical treatment of insulin-dependent diabetes mellitus and its complications. Khirurgiia (Mosk) 1996;2:81–3.

[20] Shraer TI, Rozina NS. Late results of pancreatic blood outflow deportalization and its significance in the combined modality treatment of diabetes mellitus. Probl Endokrinol (Mosk) 1992;38(5):49–52.

[21] Torgunakov SA, Torgunakov AP. Possible causes of thrombus-related hazard of a distal splenorenal venous anastomosis. Angiol Sosud Khir 2010;16(4):184–8.

[22] Torgunakov AP. Renoportal venous anasomosis. Kemerovo: Medical Institute; 1992.

[23] Ivanov PA, Golikov PP, Shcherbiuk AN, Gvakhariia GN, Syromiatnikova ED, Guliaev VA, et al. Characteristics of the postoperative period in diabetes mellitus type 1 in patients with distal splenorenal anastomosis. Sov Med 1990;2:17–9.

[24] Gal'perin EI, Shraer TI, Diuzheva TG, Kuzovlev NF, Bol'shakova TD. Experimental basis and initial clinical experience with the surgical treatment of diabetes mellitus. Khirurgiia (Mosk) 1987;2:64–70.

[25] Gal'perin EI, Diuzheva TG, Kuzovlev NF, Bol'shakova TD, Gitel' EP. Surgical correction of metabolism in diabetes mellitus. Khirurgiia (Mosk) 1988;9:6–11.

[26] Putintsev AM, Shraer TI, Sergeev VN, Maslov MG, Strukova OA. Variants of surgical management for severe arterial hypertension combined with type 2 diabetes mellitus. Angiol Sosud Khir 2010;16(2):120–5.

[27] Gal'perin EI, Kuzovlev NF, Diuzheva TG, Aleksandrovskaia TN. Approaches to surgical treatment of diabetes mellitus (experimental study). Khirurgiia (Mosk) 1983;1:13–20.

[28] Williams G, Pickup JC. Handbook of diabetes. 2nd ed. Oxford: Blackwell Science; 1999.

[29] Severgina ES, Diuzheva TG, Razgulina LE, Stakheev IB. Is localization of B-cells in the acini a normal condition or the sign of compensatory process in insulin-dependent diabetes mellitus? Arkh Patol 1992;54(12):18–23.

[30] Severgina E, Dyuzheva T, Paltsev M. Acinar B-cells in pancreas in insulin-dependent diabetic patients. The right to exist. Pathol Res Pract 1993;189(3):298–9.

[31] Severgina ES, Ponomarev AB, Diuzheva TG, Shestakova MV, Maiorova EM. Diabetic glomerulosclerosis–a prolonged stage of diabetic glomerulopathy. Arkh Patol 1994;56(4):50–5.

[32] Rosai J. Rosai and Ackerman's surgical pathology. Edinburgh: Mosby; 2004.

[33] Spencer J, Peakman M. Post-mortem analysis of islet pathology in type 1 diabetes illuminates the life and death of the beta cell. Clin Exp Immunol 2009;155(2):125–7.

[34] Richardson SJ, Morgan NG, Foulis AK. Pancreatic pathology in type 1 diabetes mellitus. Endocr Pathol 2014;25(1):80–92.

[35] Severgina ES, Ponomarev AB. Patho- and morphogenesis of diabetes mellitus and early diabetic nephropathy. Arkh Patol 1988;50(4):80–5.

[36] Atkinson MA. Pancreatic biopsies in type 1 diabetes: revisiting the myth of Pandora's box. Diabetologia 2014;57(4):656–9.

[37] Babichev SI, Kharlampovich SI, Tarasova LB, Smakov GM, Savchenko ZI. Partial denervation of the lungs in bronchial asthma. Khirurgiia (Mosk) 1985;4:31–5.

[38] Ministry of Health of RSFSR. Indications and contraindications for the surgical treatment of bronchial asthma. Moscow; 1988.

[39] Smakov GM. Complications of surgical treatment of patients with bronchial asthma. Khirurgiia (Mosk) 1990;2:124–7.

[40] Gudovskii LM, Karashurov SE, Karashurov ES, Volkov AA, Parshin VD. Surgical treatment of bronchial asthma. Khirurgiia (Mosk) 2002;7:14–8.

[41] Babichev SI, Batishchev NG, Bareisha VM. Surgical treatment of bronchial asthma. Khirurgiia (Mosk) 1972;48(12):52–6.

[42] Babichev SI, Batishchev NG. Morphological changes in lung tissue in bronchial asthma. Khirurgiia (Mosk) 1972;48(3):49–52.

[43] Meshalkin EN. 1st attempts of surgical treatment of bronchial asthma by the pulmonary autotransplantation method. G Ital Mal Torace 1968;22(1):15–22.

[44] Babichev SI, Evdokimov AI, Smakov GM, Plaksin LN. Preparation of bronchial asthma patients for bronchoscopic examinations. Khirurgiia (Mosk) 1982;7:63–7.
[45] Kavuru MS, Dweik RA, Thomassen MJ. Role of bronchoscopy in asthma research. Clin Chest Med 1999;20(1):153–89.
[46] Pol'ner AA, Kuzin II , Ermolin GA, Kurmanova LV, Sotnikova NS. Bronchial secretion immunoglobulins in bronchial asthma and chronic bronchitis. Sov Med 1984;6:36–9.
[47] Smakov GM, Evdokimov AI, Baskova OV. Prognostication of the effect of therapeutic bronchoscopy in patients with bronchial asthma according to the state of local immunity. Klin Med (Mosk) 1995;73(5):76–7.
[48] Mirrakhimov MM, Brimkulov NN, Liamtsev VT, Belov GV. Changes in the surface activity of bronchoalveolar washings and their cellular composition in bronchial asthma. Ter Arkh 1987;59(3):31–6.
[49] Nepomnyashchikh GI, Aidagulova SV, Trubnikova NV, Volkova DV, Bakarev MA. Structural modifications of the bronchial epithelium in asthma. Bull Exp Biol Med 2007;143(4):483–7.
[50] Fedoseev GB, Emel'ianov AV, Goncharova VA, Malakauskas KK, Emanuél' VL, Sinitsyna TM, et al. Bivalent cations of the bronchial contents in the pathogenesis and clinical picture of bronchial asthma. Ter Arkh 1992;64(12):58–62.
[51] Gerasin VA, Palamarchuk GF, Kizela AP. The fiber bronchoscopic evaluation of the bronchial inflammatory changes and hyperreactivity in bronchial asthma patients. Ter Arkh 1994;66(3):15–9.
[52] Ogorodova LM, Selivanova PA, Gereng EA, Bogomiakov VS, Volkova LI, Pleshko RI. Pathomorphological characteristics of unstable bronchial asthma (brittle phenotype). Ter Arkh 2008;80(3):39–43.
[53] Ovcharenko SI, Romanova LK, Filippov VV, Mladkovskaia TB. The clinicocytological parallels in exacerbated bronchial asthma. Ter Arkh 1992;64(1):54–8.
[54] Novikova AV, Klimanskaia EV, Shershevskaia AI, Erdes SI, Sosiura VKh, Taberovskaia EM. The immunomorphology of the mucosa of the bronchi and gastroduodenal zone in children with combined disease of the bronchi and gastrointestinal tract. Arkh Patol 1996;58(6):12–6.
[55] Grinshtein Iul, Shestovitskii VA. Severe bronchial asthma in elderly patients. Adv Gerontol 2004;13:102–6.
[56] Mavritsin LE, Lifshits NA. Complications in the fiber bronchoscopy of bronchial asthma patients. Klin Med (Mosk) 1980;58(4):37–40.
[57] Budkova AA, Volkova LI, Budkov SR, Bogomiagkov VS. Clinicomorphological assessment of budesonide efficiency in patients with bronchial asthma. Ter Arkh 2003;75(8):48–51.
[58] Jargin SV. Unnecessary operations: a letter from Russian pathologist. Int J Surg 2010;8(5):409–10.
[59] Murphy J, Jargin S. International perspectives and initiatives. The state of medical libraries in the former Soviet Union. Health Info Libr J 2010;27(3):244–8.
[60] Jargin SV. Barriers to the importation of medical products to Russia: in search of solutions. Healthc Low-resource Settings 2013;1:e13. http://pagepressjournals.org/index.php/hls/article/view/728 [accessed 08.06.14].
[61] Goss PE, Strasser-Weippl K, Lee-Bychkovsky BL, Fan L, Li J, Chavarri-Guerra Y, et al. Challenges to effective cancer control in China, India, and Russia. Lancet Oncol 2014;15(5):489–538.
[62] Kovanov VV. Operative surgery and topographic anatomy. Moscow, Russia: Meditsina; 1995.
[63] Good Clinical Practice. National Standard of Russian Federation GOSTR 52379-2005, introduced on April 1, 2006. http://www.medtran.ru/rus/trials/gost/52379-2005.htm [accessed 08.06.14].
[64] Guideline for good clinical practice E6(R1). Current Step 4 version dated 10 June 1996. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 1996. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf [accessed 20.09.14].
[65] Ivaniushkin AIa. Biomedical ethics. Moscow: Avtorskaya academia; 2010.

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