

UDC 615.1:658.7

A.G. Khromykh, O.V. Posylkina, M.I. Sydorenko

National University of Pharmacy

**METHODOLOGICAL APPROACHES TO ESTIMATION AND
MANAGEMENT OF CONTRACT RESEARCH ORGANIZATIONS'
LOGISTIC RISKS IN CLINICAL TRIALS SPHERE**

ABSTRACT

Logistic risks appropriate to contract research organizations (CRO) in clinical trials (CT) had been defined in the article. The necessity to consider logistic risk management process as separate sub-process in CRO activities had been accentuated. Recommendations on logistic risk management and methodological assessment tools had been justified.

Keywords: logistics, clinical trials, clinical logistics, logistic risks, pharmaceutical branch.

Problem statement. As worldwide practice shows, quality, effectiveness and efficiency of CRO activities in CT mostly depend on reasonable logistic strategy and logistics-based management. Logistic approach in management allows increasing both profit and quality of logistic service, guarantying effectiveness of CRO flow processes management in order to get more competitive advantages in world CT market [1, 14, 15].

According to the research, today world CT market is about 50 – 80 billion dollars and increases [5, 13, 16].

According to the PMR «Clinical trials in CIS countries 2012 — Russia, Ukraine, Belarus and Georgia. Development forecasts for 2012–2014», CIS common CT market in 2011 amounted to 429 million euros, which is 19% more than in 2010. The most share of the market belongs to Russia – 63%. Ukrainian share of the market is about 33%. According to the PMR forecast, CIS CT market increase will amount to 14% per year, and by 2014 the market will reach 712 million euros [5, 7].

Stakeholders involved in CT are: sponsor, CRO, researchers, medical institutions and patients. Mostly, pharmaceutical companies are sponsors of CT. In that case pharmaceutical companies conduct CT on their own or make it outsource [6, 7, 10, 11]. Though, some projects are financed by academic institutions and research centers.

The analysis showed that while assessing and choosing the CRO, sponsoring agency should base on methodological approaches and take into account certain criteria. GMP states that sponsoring agency is responsible for both assessment the CRO possibility to perform the work successfully and inclusion into the contract provisions that guarantee the compliance with GMP principles. So, choosing the CRO should be based on quality assurance system and on CRO risk analysis system in particular [1, 10].

So far as quality and effectiveness of logistic services influences the CT quality and effectiveness, it becomes necessary to develop the methodological approaches to assessment of logistic risks, which affect the CRO competitive ratio.

Recent research and publications analysis. Scientific approaches to CRO logistic risk management in CT today are not of widespread. This is why these problems are not covered either in domestic or in foreign publications. Domestic scientists who studied some aspects of the development and practical application logistic risks management tools and assessing methods are Gadjinsky O.M., Kal'chenko O.S., Kozlovsky V.O., Romanov V.S., Yenchenko Ye.V., Trydid O.M., Revenko V.L. and others [2, 4]. Some aspects of pharmaceutical companies' risks identification and assessment had been covered in papers [3, 8, 9, 12].

Unsolved aspects of common problem definition. Scientific justification of different aspects of logistic activity in pharmaceutical branch today is very important. But such problems as identification and classification of CRO risks, that influence the CT quality, effectiveness and efficiency, are still unsolved.

Formulation of article aims. The aim of this paper is to justify the risk management algorithm for CRO logistic activities in order to ensure the certain quality and effectiveness of CT. Achieving this goal requires the essence

disclosure of the notion «CT logistic risks management», investigation of risks types in different logistic activities of CRO, justifying recommendations on improvement the logistic risks management and methodological assessment tools.

Presentation of the main research. According to the scientific data, risk management is a set of methods, techniques and activities to predict the occurrence of risk events and to take timely measures to mitigate them [1, 2]. As for CRO logistic risks, their management should be performed taking into account the specifics of clinical logistics with further adaptation of general management methods and tools. The suggested algorithm of CRO logistic risk management is shown at fig.1.

Literature and Internet sources analysis shows that methodological tools used for risk level assessment are extensive. But the experts consider correlation analysis the most effective among them [2].

Most logistic risks appropriate to CRO activities are conditioned by integrated risk factors, which, as opposed to local factors, affect two or more risks at a time. That is why in aggregated assessment of all logistic risks in CRO activities the interdependency of identified logistic risks should be taken into account. These interdependencies could be essential or non-essential. Traditionally, they consider essential if correlation index (CI) is more than 0.75 and non-essential if the index is less than 0.25 [2].

If the interdependency is very essential ($CI > 0.75$), the CRO logistic risks aggregate (AR) could be calculated as the sum of these risks costs. And the cost of each logistic risk (R) should be calculated according to the classic risk theory as the mathematical expectation of possible loss:

$$AR = \sum_{i=1}^N R_i = \sum_{i=1}^N p_i U_i, \quad (1)$$

If the interdependency is non-essential ($CI < 0.25$), the CRO logistic risks aggregate (AR) could be calculated as follows:

$$AR = \sqrt{\sum_{i=1}^N R_i^2} = \sqrt{\sum_{i=1}^N (p_i \times U_i)^2}, \quad (2)$$

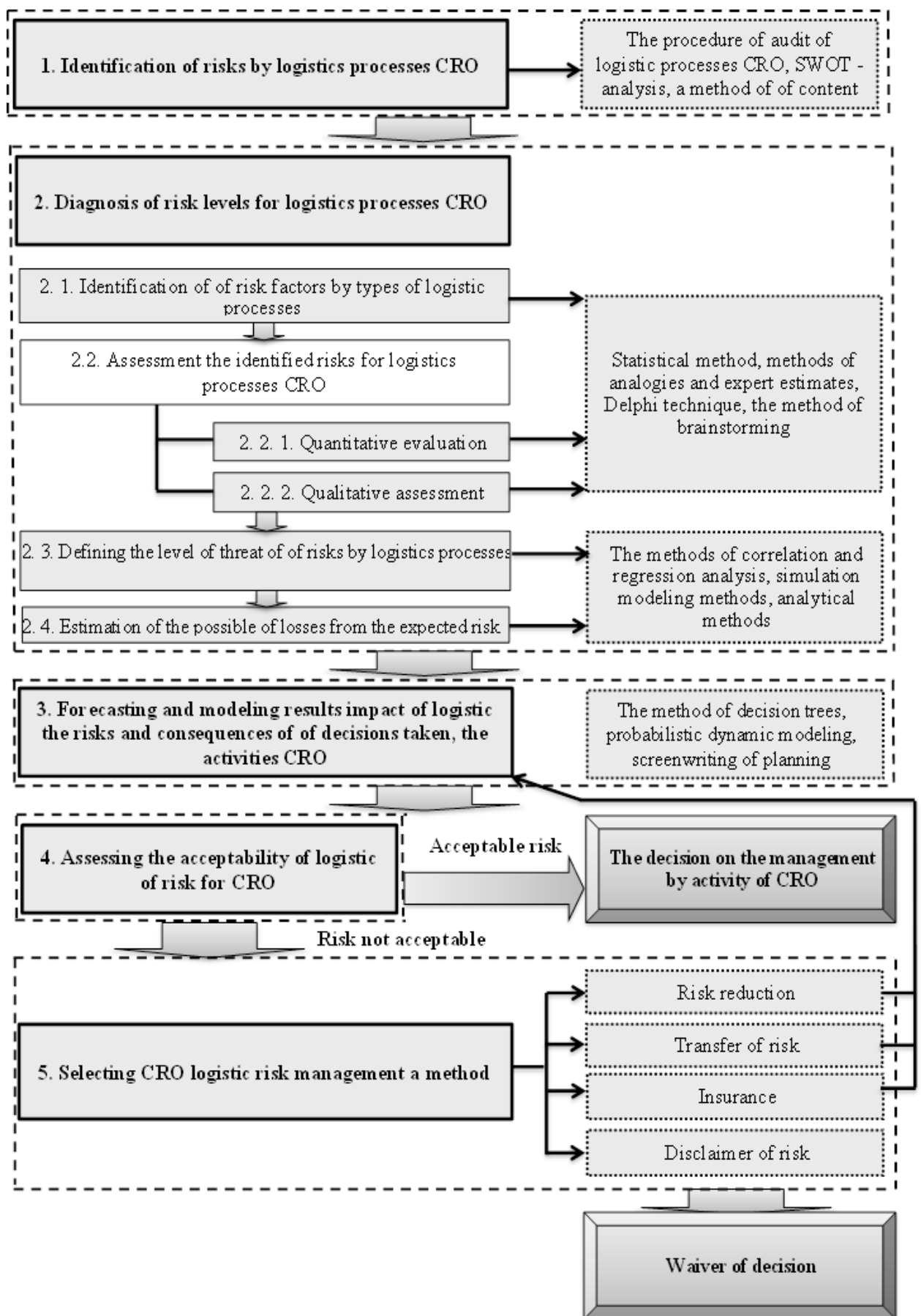


Fig.1. The algorithm of risk management and rational managerial decisions making in CRO logistic activity

where: AR - logistic risks aggregate in analyzed period; R_i – the value of i -s logistic risk in analyzed period; U_i – the loss from the i -s logistic risk in analyzed period; p_i – the probability of i -s logistic risk in analyzed period.

If the interdependency is essential ($0.25 < CI < 0.75$), the CRO logistic risks aggregate (AR) could be calculated as follows:

$$AR = 2\sqrt[N]{\sum_{i=1}^N kk_{ij} R_i R_j} = 2\sqrt[N]{\sum_{i=1}^N kk_{ij} (p_i \times U_i) \times (p_j \times U_j)}, \quad (3)$$

where: R_i, R_j – costs of i -s and j -s CRO logistic risks in analyzed period, respectively; p_i, p_j - probabilities of i -s and j -s CRO logistic risks in analyzed period, respectively; U_i, U_j - losses from the i -s and j -s CRO logistic risks in analyzed period, respectively; kk_{ij} – i -s and j -s CRO logistic risks correlation indexes in analyzed period. In case when $i=j$, pair correlation index equals +1, i and j are order numbers of CRO logistic risks in analyzed period.

By loss from the logistic risk we mean possible increase of expected costs for the provision of clinical center with essential medicines and biological samples in certain quantity and assortment at certain time, when all logistic processes are in compliance with GxP requirements [1, 5].

By logistic risk management effect we mean decrease of the logistic risk aggregate or of the mathematical expectation of expected costs associated with CT possible increase. That is why each logistic risk should be investigated for its manageability in order to create effective managerial measures [2, 5].

Let's consider an example that shows the practical value of suggested methodological recommendations implementation. Research had been carried out on the basis of logistic services market monitoring made by Association of Clinical trials organizations [7]. In order to identify the most essential risk factors in CRO activities, which affect their competitive ratio, the expert method had been used. The inquiry form had been developed and clinical logistics experts had been asked to complete it. Basing on the research results and taking into account ISO and GxP requirements, there had been identified following list of logistic risks by the types of CRO logistic activities affecting the CT quality, effectiveness and efficiency (fig. 2).

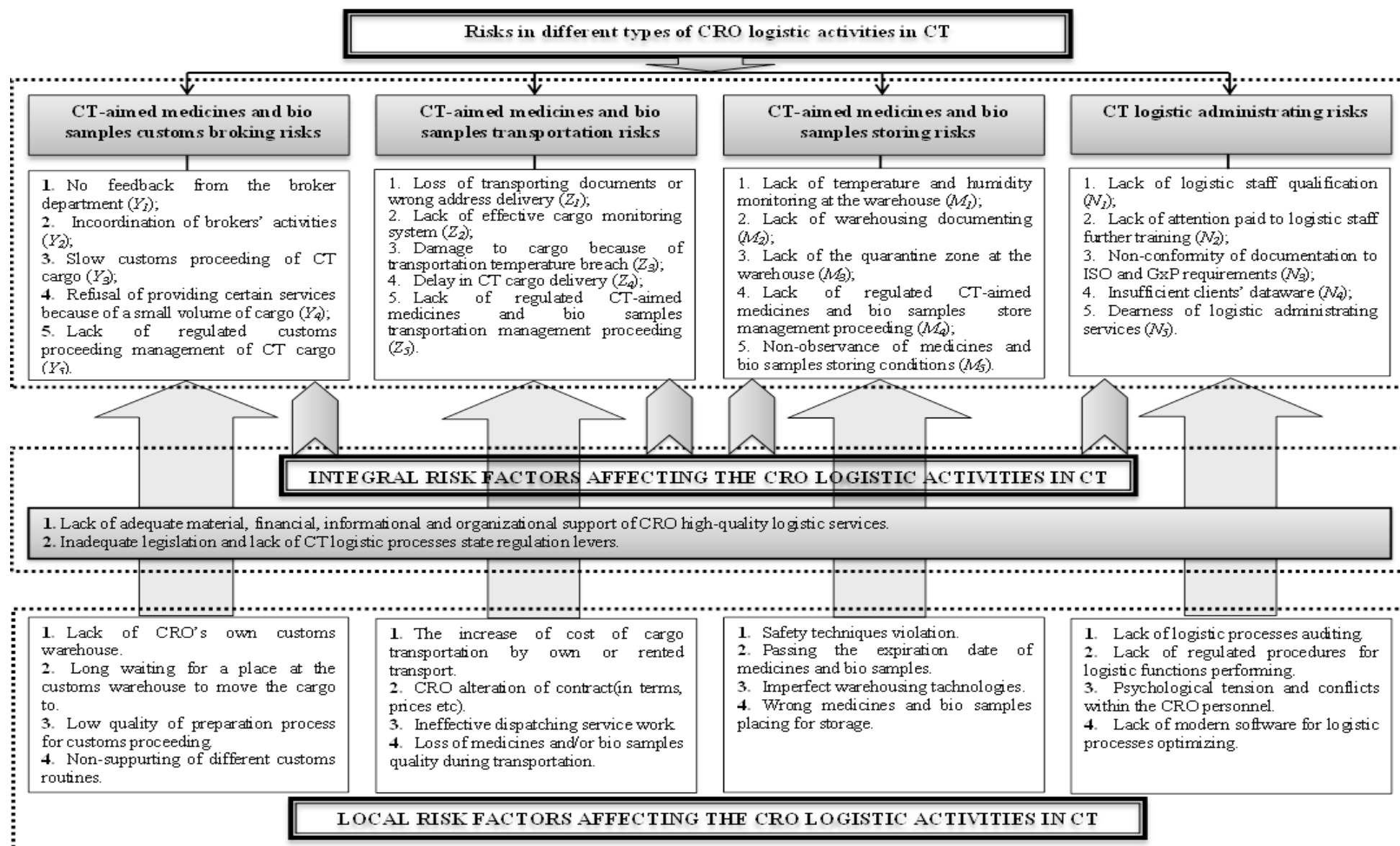


Fig. 2. Risks in different types of CRO logistic activities in CT

The logistic risks' influence weight evaluation had been carried out on a five-point scale. Risks with the evaluation of more than 3 points are considered to be the most influent and risks with the evaluation of more than 3 points are considered to be the less influent on the quality of CRO logistic activity.

As the result of data processing density histograms of logistic risks significance had been built: a) risks associated with customs broker processes during medicines and bio samples import/export for CT needs; b) CT-aimed medicines and bio samples transportation risks; c) CT-aimed medicines and bio samples storing risks; d) CT logistic administrating risks (fig. 3).

The concordance of experts' opinions had been confirmed by calculating the relevant indexes.

Thereby, it is arguable that CRO logistic activities are most negative influenced by: slow customs proceeding of CT cargo (Y_3); delay in CT cargo delivery (Z_4); non-observance of medicines and bio samples storing conditions (M_5); lack of logistic staff qualification (N_1) etc.

Research had made it possible to identify 24 risk factors in CRO activities, including 16 local and 2 integral, which cause foregoing logistic risks. Each logistic risk depends on a specific set of risk factors, and their sum may exceed the common amount of identified risk factors [2, 6, 13, 16].

The correlation ratio calculated by four types of logistic risks in investigated CRO equals 0.33. Logistic risks aggregate for investigated CRO had been calculated by the data given in the table 1 [7].

Table 1

Basic data for assessment of CRO logistic risks in CT

Risk	Probability	Loss, mln UAH	Risk factors		
			In all	Integral	Local
Slow customs proceeding of CT cargo	0,2	2,5	6	2	4
Delay in CT cargo delivery	0,4	2	6		4
Non-observance of medicines and bio samples storing conditions	0,3	1,5	6		4
Lack of logistic staff qualification	0,1	0,5	6		4
In all	-	-	24		16

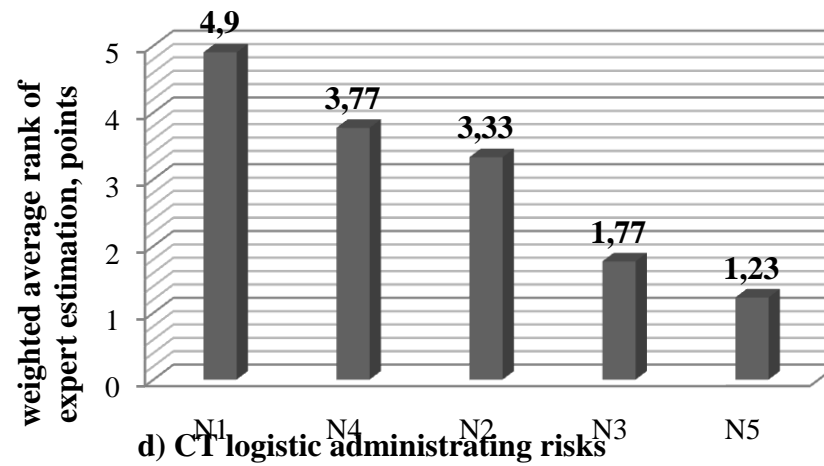
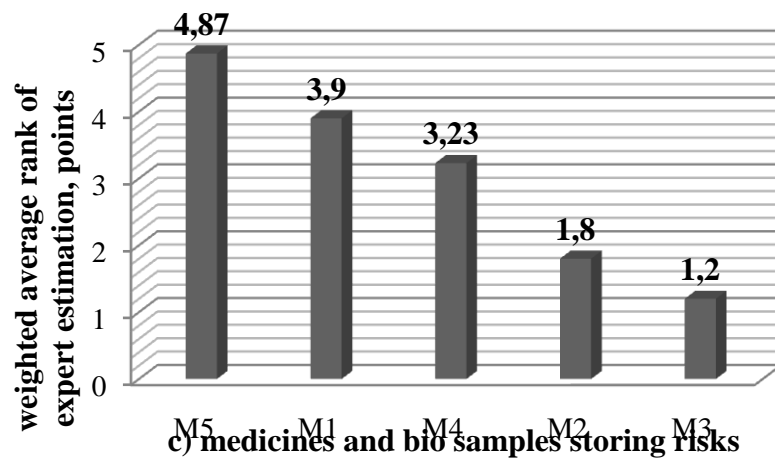
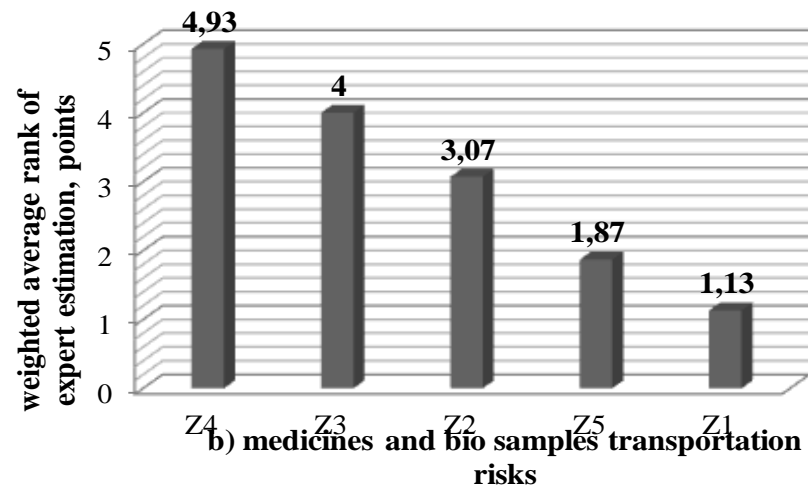
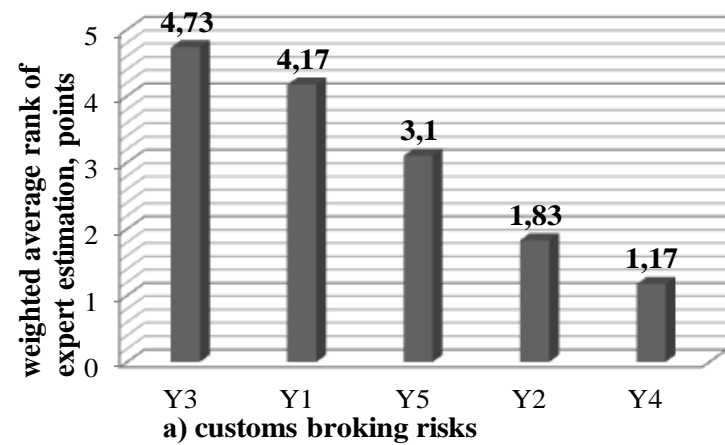


Fig. 3. Density histograms of CRO logistic risks significance in CT

The calculated aggregate of identified entry risks (AR_e) in considered example equals 1.1 million UAH.

There had been developed specific measures to manage essential logistic risks in CRO (table 2).

Table 2

Measures to manage essential CRO logistic risks in CT

Risk	Management measures	Entry level			Residual level		
		Entry probability	Entry loss	Weighted average of risk	Residual probability	Residual loss	Weighted average of risk
Slow customs proceeding of CT cargo	Customs brokers diversification	0.2	2.5	0.5	0.2	1.5	0.3
Delay in CT cargo delivery	Limiting the CRO activity	0.4	2	0.8	0.4	1	0.4
Non-observance of medicines and bio samples storing conditions	Insurance in case of non-observance of medicines and bio samples storing conditions	0.3	1.5	0.45	0.3	0.8	0.24
Lack of logistic staff qualification	Assignment of risk by qualifying logistic staff	0.1	0.5	0.05	0.1	0.3	0.03
Logistic risks aggregate, mln UAH		1.1			0.6		

The calculated aggregate of residual risks (AR_r) in considered example equals 0.6 million UAH.

Thereby, implementing of suggested methodological approaches to CRO logistic risk management in CT provides economic effect in the amount of 0.5 million UAH.

Summing up the above, it is arguable that application of suggested CRO logistic risk management methodology allows to:

1. Provide scientific basis for improving the CT logistic risk management.
2. Increase the relevance of process approach in analyzing of logistic risks, planning of managerial measures; facilitates monitoring and control of CRO logistic risk management efficiency.
3. Increase CRO management's responsibility as risk-managers at each management level.

4. Advantage the rational distribution of CRO financial resources in CT logistic activities [6, 8, 9, 12, 16].

Conclusions and further research prospects. Taking into account results of the research carried out, the following conclusions can be made:

1) Ukrainian CT market investigation had proved that it is necessary to develop the methodological approaches to management of logistic risks, that affect CRO competitive ratio in CT.

2) Main risks in clinical logistics had been identified and CRO logistic risk management algorithm had been suggested.

3) It had been proved that suggested methodological approaches to logistic risks management in CRO activities allow to make reasonable managerial decisions in order to make resource use more rational, reduce possible loss and improve the quality of logistics processes in CT conducted.

References:

1. Белоусов Д.Ю. Кризис – менеджмент клинических исследований / Д.Ю. Белоусов. – [электронный ресурс]. – Режим доступа к сайту: <http://www.cbio.ru/modules/news/article.php?storyid=1945>.

2. Бродецкий Г.Л. Управление рисками в логистике: учеб. пособие для студ. учрежд. высш. проф. образ. / Г.Л. Бродецкий, Д.А. Гусев, Е.А. Елин. – М.: Изд. Центр «Академия», 2010. – 192 с.

3. Громовик Б.П. Характеристика факторов современной внешней среды фармацевтической организации / Б.П. Громовик, С.М. Мокрянин // Провизор. – 2007. - № 19 – С. 14-18.

4. Логістичний менеджмент фармацевтичного виробництва: моногр. / О. В. Посилкіна, Р. В. Сагайдак-Нікітюк, Г. В. Загорій та ін.; за заг. ред. О. В. Посилкіної. – Х. : Вид-во НФаУ, 2011. – 772 с.

5. Лукьянчук Е. Мировой рынок клинических исследований / Е.Лукьянчук. - [электронный ресурс]. - Режим доступа к сайту: <http://www.apteka.ua/article/158875>.

6. Мальцев В.И., Ефимцева Т.К., Белоусов Ю.Б. и др. Клинические испытания лекарств / Под ред. В.И. Мальцева, Т.К. Ефимцевой, Ю.Б. Белоусова, В.Н. Коваленко. - 2-е изд., перераб. и доп. - К.: Морион, 2006. - 456 с.

7. Мониторинг рынка логистических услуг - Ассоциация организаций по клиническим исследованиям. - [электронный ресурс].- Режим доступа к сайту: http://acto-russia.org/index.php?option=com_content&task=view&id=81.

8. Мнушко З.М. Оцінка впливу факторів макросередовища на роботу аптечних закладів / З.М. Мнушко, І.В. Підліснюк, І.В. Пестун // Вісник фармації. - 2008. - № 2 (54). - С. 34-37.

9. Пестун І.В. Методика прогнозування рівня розвитку аптечних підприємств за оцінками факторів мікросередовища / І.В. Пестун, І.В. Бондарєва, З.М. Мнушко, М.М. Нессонова // Клиническая информатика и Телемедицина. - 2010. - Т. 6, № 7. - С. 125-132.

10. Посилкіна О.В. Актуальні проблеми розвитку клінічної логістики в Україні / О.В. Посилкіна, І.А. Зупанець, А.Г.Хромих // Управління, економіка та забезпечення якості в фармації. - 2012. - № 2 (22). - С. 78-85.

11. Посилкіна О.В. Методичні засади оцінки ефективності діяльності і конкурентоспроможності контрактно-дослідних організацій з надання логістичних послуг у сфері клінічних досліджень / О.В. Посилкіна, І.А. Зупанець, А.Г.Хромих, В.В. Ніколаєва // Клінічна фармація. - 2012. - Т. 16, № 4. - С. 17-24.

12. Посилкіна О.В. Методика управління логістичними ризиками в умовах фармацевтичної галузі / О.В. Посилкіна, Р.В. Сагайдак - Нікітюк // Фармаком. - 2009. - № 3. - С. 62-67.

13. Annual Review of Contract Research Organisations/European Pharmaceutical Contractor, Spring 2002. – [Internet resource]. – Access mode to a site:www.samedanltd.com/members/archives/EPC/Spring2002/MarianeOneill.html.

14. Jayashree W. Clinical Research Outsourcing Overview, Current Scenario&Future Outlook/International Biopharmaceutical Association Publication newsletter, April, 2005. – P. 112-118.

15. Mayrhofer U. International market entry: does the home country affect entry-mode decisions? // Journal of International Marketing. – 2004. – Vol. 12. № 4.

16. Porter W., Krivavic S. The CRO Advantage: Outsource Clinical Trials To Launch Biotech Development Success/BioPharm International, June 2005. – [Internet resource]. – Access mode to a site:
www.biopharminternational.com/biopharm/article/articleDetail.jsp?id=166175