2017/2018

Univerza v Mariboru

Medicinska fakulteta

UČNI NAČRT PREDMETA / COURSE SYLLABUS	
Predmet:	**Metode raziskovalnega dela v medicini z medicinsko statistiko**
Course title:	**Methods of research work in medicine with medical statistics**

Študijski program in stopnja Study programme and level	Študijska smer Study field	Letnik Academic year	Semester Semester
Splošna medicina		**1.**	**2.**
Medicine			

Vrsta predmeta / Course type

Univerzitetna koda predmeta / University course code:

Predavanja Lectures	Seminar Seminar	Sem. vaje Tutorial	vaje work	Teren. vaje Field work	Samost. delo Individ. work	ECTS
20	**10**	**10**	**20**	**/**	**60**	**4**

Nosilec predmeta / Lecturer: Prof. dr. Pavel Skok

Jeziki / Languages:	
Predavanja / Lectures:	slovenski / slovene
Vaje / Tutorial:	slovenski / slovene

Pogoji za vključitev v delo oz. za opravljanje študijskih obveznosti:

Pogojev ni.

Prerequisits:

None.

Vsebina:

Opredelitev pojma znanosti. Razmejitev med strokovnim in raziskovalnim delom kot virom novega znanja. Spoznati splošne metode znanstveno raziskovalnega dela, pomen povezanosti teoreticnih znanj in uporabe v klinicni medicini, algoritmi odlocanja. Raziskovalno delo kot metoda preverjanja klinicnih odlocitev in odgovornega sledenja posledic. Eticna in pravna vprašanja pri raziskovanju v biomedicini, odnos med zdravnikom, farmacevtsko industrijo in bolnikom, njegova obveščenost in soodlocanje. Definiranje odnosov vzrok – posledica v biomedicini in vloga presejalnih testov.
Razumevanje osnovnih statisticnih pojmov v biomedicini (incidenca, prevalenca, pozitivna in negativna napovedna vrednost, obcutljivost in specificnost testov, lažno pozitivnih in negativnih rezultatov), pomena relativnega tveganja in razmerja obetov. Razlikovanje prospektivnih, retrospektivnih, epidemioloških, kontroliranih, randomiziranih, kohortnih, primer – kontrola in dvojno slepih vrst raziskav. Pomen racunalniške tehnologije in statisticnih orodij pri znanstveno raziskovalnem delu.

Content (Syllabus outline):

Definition of the term science. Boundaries between scientific and research work as sources of new knowledge. Common methods of scientific research, mening of liasion of theoretical knowledge and and its aplication in clinical medicine, algorithams of decision making. Research work as method of of clinical decisions and responsible consequences following-up testing. Ethical and legislative questions in biomedicne research, relationship between pfysician, pharmaceutical industry and patient's acknowledgment and codecison-making. Definiton of relationsheep cause – consequence in biomedicine and role of screening tests.
Comprehension of basic statistic terms in biomedicine (incidence, prevalence, positive and negative prognostic values, sensitivity and specificity of tests, false positive and negative results), meaning of relative risk and expectation ratio. Distinguishes between prospective, retrospective, epidemiologic, followed-up, randomised, cohort , case – control, and double blind researches. Importance of computer technology and statistic software in scientific research work. Statistical part: the research process, qualitative and

Statistični del: raziskovalni proces, kvalitativna in kvantitativna analiza podatkov osnovni statistični pojmi (vrste spremenljivk, verjetnostne porazdelitve, mere centralne tendence in mere variabilnosti), osnove statističnega sklepanja (frekvenčna porazdelitev, ničelna domneva, standardna napaka, interval zaupanja), univariatna statistična analiza (predstavitev podatkov:tabelarna, grafična), univariatni statistični testi, bivariatna statistična analiza (odvisnosti med spremenljivkama), bivariatni parametrični testi (t-test, korelacija, ANOVA, t- test za odvisne vzorce), bivariatni neparametrični statistični testi (Mann-Whitney U test, neparametrična korelacija, hi-kvadrat test, Kruskal-Wallis H test, Median test, neparametrični statistični testi za odvisne vzorce). Osnove genetike, anatomije in fiziologije laboratorijskih živali. Primerjava laboratorijskih živali in človeka, prednosti in slabosti živalskih modelov. Etika pri delu z laboratorijskimi živalmi. Osnove zakonodaje na področju laboratorijskega dela in dela z laboratorijskimi živalmi. Celični in tkivni modeli v predkliničnem raziskovanju. Gensko spremenjeni organizmi in njihova vloga v predkliničnih raziskavah. Elektro- in opto-fiziološke metode. Obdelava in statistična analiza podatkov pri predkliničnem raziskovanju. Pregled literature in dostop do znanstvene literature. Publiciranje v predkliniki. Kako povezati klinične študije in laboratorijske raziskave: temeljni principi znanstvene metodologije, orodja za pregled in analizo znanstvene literature, oblikovanje hipoteze in načrtovanje študije; objava izsledkov v obliki znanstvenih člankov Integrirani sistemi za dostop do podatkovnih zbirk na področju biomedicine: Entrez (NCBI)-PubMed, OMIM, Gene, Protein, Enseble.. Različni pristopi uporabe laboratorijskih preiskav (biokemijskih in genetskih) kot dopolnitev in nadgradnja kliničnih študij Pregled najnovejših laboratorijskih tehnologij uporabnih za klinične študije; Seminarske vaje: Metode statistične genetike za iskanje povezav genotip/fenotip Laboratorijske vaje: Analiza krvi in urina:hematološke, biokemijske in imunološke preiskave; Pretočna citometrija; Proteomske analize – Uporaba 1D/2D SDS-PAGE, Western blot, LC-MS Genetske in epigenetske analize: genska tipizacija polimorfizmov SNP, genska eskpresija sekvenciranje naslednje generacije.	quantitative data analysis, basic statistical concepts (types of variables, probability distributions, central tendency and measures of variability), basics of statistical conclusions (frequency distribution,null hypothesis, standard error, confidence interval), univariate statistical analysis (presentation of data: tables, graphs), single variant statistical tests, bivariate statistical analysis (dependence between variables), bivariate parametric tests (t - test, correlation, ANOVA, t-test for paired samples), bivariate nonparametric statistical tests (Mann - Whitney U test, non-parametric correlation, chi-square test, Kruskal - Wallis H test and the median test, nonparametric statistical tests for dependent samples). Basic genetics, anatomy and physiology of laboratory animals. Comparison between laboratory animals and humans, advantages and disadvantages of animal models. Animal research ethics. Legislation in the field of laboratory work and work with laboratory animals. Cellular and tissue models in basic medical research Genetically modified organisms and their role in basic medical research. Electrical and optical methods in basic medical research Statistical analysis of data in basic medical research. Literature review and access to scientific literature. Publishing in basic medical research. How to combine clinical studies with laboratory research: basic principals of scientific methodology, tools for literature analysis, development of hypothesis, experimental study design, publication of scientific papers and doctoral thesis; different approches for integration of laboratory analysis (biochemical, genetic) into clinical studies Integrated systems for biomedical data retrieving: ENTREZ (NCBI)-PubMed, OMIM, Gene, Protein, Ensemble... Overview of the state-of art laboratory tecnologies most relevant for intergration into clinical studies; Seminars: Statistical genetic methods for identification of genotype/phenotype corellations Laboratory: Blood and urine analysis: heamotlogical, biochemical and immunological parameters; Flow cytometry Proteomics: 1d/2D SDS-PAGE, Western blot, LC-MS Genetic analysis: genotyping of SNPs, gene expression, next generation sequencing

Temeljni literatura in viri / Readings:

1. Beauchamp TL, Childress JE. Principles of biomedical ethics, 5th ed. Oxford University Press, Oxford 2001.
2. Norman K. Denzin (Editor), Yvonna S. Lincoln (Editor) Handbook of Qualitative Research,2nd ed. Sage publications, London 2000.
3. Altman DC. Practical statistics for medical research. Chapman&Hall. London 1996.
4. Matthews DE, Farewell VT. Using and understanding statistics. Karger, Basel, 1996.
5. Adamič Š. Temelji biostatistike, Medicinska fakulteta Ljubljana, 1989.
6. Hau J. and Van Hoosier G. L.: Handbook of laboratory animal science. Third edition, Volume I, II and III. CRC Press, 2010-2013.
7. Fox. J.G.: The mouse in biomedical research. Second edition. Volume I & II. Academic Press, 2006.
8. Ed. Popesko P., Rajtova V., Horak J.: Anatomy of small laboratory animals. Vol. 2. Wolfe publishing, 1992.
9. Molleham A. Patch Clamping An Introductory Guide to Patch Clamp Electrophysiology. Wiley & Sons, 2003.
10. Pawley J. Handbook of Biological Confocal Microscopy. Third edition. Springer, 2006.
11. Zakon o zaščiti živali (uradno prečiščeno besedilo) (ZZZiv-UPB3),Uradni list RS, št. 38/2013 z dne 3. 5. 2013.
12. Pravilnik o pogojih za izvajanje poskusov na živalih. Uradni list RS, št 37/2013, 29. 4. 2013.
13. Field A. Discovering statistics using SPSS. 3rd ed. SAGE Publications, 2009.
14. Glantz SA. Primer of biostatistics. 6th edition. McGraw-Hill, 2005.
15. Župančič A. O. O ustvarjalnosti v znenstvenem raziskovanju. ZRC SAZU, 2006.
16. Robert Nussbaum, Roderick McInnes, Huntington Willard. Thompson & Thompson Genetics in Medicine. 8th ed., Philadelphia :Elsevier, 2015

Cilji in kompetence:

Poglavitni cilj predmeta je pridobitev nekaterih teoretičnih znanj in praktičnih veščin, ki jih potrebuje raziskovalec pri raziskovalnem delu v biomedicini.
Razumeti pomen znanosti in pogojev za raziskovalno delo ter ustvarjanje novega znanja. Ustvariti razmišljujoc odnos do raziskav v biomedicini, molekularni biologiji, genski tehnologiji, fiziologiji, anatomiji. Spoznati osnove raziskovalnega dela v biomedicini in bioznanostih, povezavo in pomen epidemiologije, biostatistike in njenih orodij (statisticnih testov, vrednotenja), vloga izsledkov na odločanje.

Študenti bodo znali na osnovi pregleda znanstvene literature ugotoviti trenutno stanje znanja na področju določene biomedicinske problematike, odkriti še neodgovorjena relevantna znanstvena vprašanja, postaviti hipotezo in načrtovati biomedicinsko študijo, ki bo ustrezno ovrednotila hipotezo. Študenti bodo sposobni napisati in izvesti raziskovalni projekt s katerim bodo odgovorili na določena klinična vprašanja s pomočjo rezultatov biokemijskih in genetskih laboratorijskih preiskav.
Študenti bodo poznali in razumeli delovanje najpomembnejših tehnologij za raziskovanje na področju biomedicine, predvsem biokemije in genetike, in bodo znali uporabiti tehnologije za reševanje relevantnih kliničnih vprašanja.

Objectives and competences:

The major aim of the course is to gain the theoretical knowledge and practical skills needed for a researcher in biomedical research. Understanding the meaning of science and research work conditions and new knowledge acquiring. Establishment of contemplative approach to researches in biomedicine, molecular biology, genetictechnology, physiology, anatomy. Acquiring of basic knowledge about researching in biomedicine and biosciences, relationship and importance of epidemiology, biostatistics and their tools (statistic tests, evaluation) importance of findings for decision making.
Students will be able to perform systematic review of scientific literature and to establish the state–of-art in the specific biomedical research topic. Students will be able to identify relevant open scientific questions, to set the apropriate hypothesis and to design biomedical study to evaluate the hypothesis. Students will be able to write and execute the research project to answer specific clinical questions using the results from biochemical and genetic laboratory investigations.

Students will understand the working the state-of-art laboraty technology most relevant for biomedical research, including biochemistry and genetics, and will be able to use the technology to adress relevant clinical issuses.

Predvideni študijski rezultati:

Znanje in razumevanje: pomena znanosti, kriticnega vrednotenje izsledkov raziskav v biomedicini in preverjanje domnev. Zavedanje možnih napak pri analizah, sklepanju in prikazovanju rezultatov. Sposobnost analize znanstveno raziskovalnih prispevkov, vsebinska in kvalitativna.

Intended learning outcomes:

Knowledge and understanding: knowledge and understanding of science, critical assessment of the research results in biomedicine and hypothesis testing. Awareness of possibility of false analyse results, conclusions and result presentation. Ability of scientific research contributions, content and quality analyse.

Prenesljive/kljucne spretnosti in drugi atributi: Nacrtovanje raziskave, pomen natancnosti in tocnosti pri zbiranju podatkov in izvajanju raziskave, obdelava in kvantitativna/kvalitativna interpretacija pridobljenih rezultatov v skladu z znanimi dejstvi in pridobljenimi novimi spoznanji.	Transferable/Key Skills and other attributes: research planning, meaning of precision and accuracy in data collection, carrying out of the research, data processing, quantitative and qualitative interpretation of results according to known facts and new findings.

Metode poučevanja in učenja:	**Learning and teaching methods:**
interaktivna predavanja E-učenje problem-based seminars praktične vaje	Interactive lectures E-learning problem-based seminars practicals

Načini ocenjevanja:	Delež (v %) / Weight (in %)	**Assessment:**
Način (pisni izpit, ustno izpraševanje, naloge, projekt) ŠTUDIJSKE OBVEZNOSTI ŠTUDENTOV Glede na sklep Senata z dne 13. 6. 2011 je za študente obvezna 50 % udeležba na predavanjih. POGOJI ZA PRISTOP K POSAMEZNEMU PREVERJANJU ZNANJA: opravljen seminar in vaje.		Type (examination, oral, coursework, project): ACADEMIC OBLIGATIONS OF STUDENTS According to the decision of the Senate on June 13, 2011, 50% attendance at lectures is obligatory for students. REQUIREMENTS FOR ACCESS TO INDIVIDUAL KNOWLEDGE CHECKING: completed seminar assignment and exercises
Računalniški izpit	**100 %**	**Computer exam**

Reference nosilca / Lecturer's references:

1. Repnik K, Koder S, **Skok P,** Ferkolj I, Potočnik U. Transferrin level before treatment and genetic polymorphism in HFE gene as predictive markers for response to adalimumab in Crohn's disease patients. *Biochemical genetics*, 2016, str. [1-11].
2. Zupančič K, Skok K, Repnik K, Weersma RK, Potočnik U, **Skok P.** Multi-locus genetic risk score predicts risk for Crohn's disease in Slovenian population.*World journal of gastroenterology* 2016, vol.22,issue 14, str. 3777-3784.
3. Gorenjak M, Škorjanc D, **Skok P.** Lactobacillus plantarum PCS 26 as a probiotic dietary supplement in Slovenian patients with metabolic syndrome:a pilot clinical study. *Acta medico-biotechnica* 2015, vol. 8, [no.] 2, str. 23-31.
4. Koder S, Repnik K, Ferkolj I, Pernat Drobež C, **Skok P,** Weersma RK, Potočnik U. Genetic polymorphism in ATG16L1 gene influences the response to adalimumab in Crohn's disease patients. *Pharmacogenomics*, 2015, vol. 16, no. 3, str. 191-204.
5. Gorenjak M, Gradišnik L, Trapečar M, Pistello M, Pinto Kozmus C, Škorjanc D, **Skok P,** Langerholc T, Cencič A. Improvement of lipid profile by probiotic/protective cultures:study in a non-carcinogenic small intestinal cell model. *The New microbiologica*, 2014, vol. 37, no. 1, str. 51-64.
6. Popovič P, Zore A, Šurlan Popovič K, Garbajs M, **Skok P.** Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in patients with recurrent variceal hemorrhage. Gastroenterology Research and Practice, ISSN 1687-630X. [Online ed.], 2013.http://www.hindawi.com/journals/grp/2013/398172/cta/,doi: 10.1155/2013/398172.
7. Gorenjak M, **Skok P,** Cencič A. Novel promising functional cell models to study molecular events in metabolic syndrome. Nutritional therapy & metabolism, ISSN 1828-6232, 2012, letn. 30, št. 1, str. 34-41.
8. **Skok P**, Sinkovič A. Upper gastrointestinal haemorrhage: predictive factors of in-hospital mortality in patients treated in the medical intensive care unit. J Int Med Res. 2011;39(3):1016-27.
9. Povalej P, Verlič M, Štiglic G. Discovery systems. V: MEYERS, Robert A. (ur.). *Encyclopedia of complexity and systems science*. New York: Springer, cop. 2009, vol. 2, str. 1982-2002.
10. Štiglic, G, Povalej P, Fijačko N, WANG F, Kalousis A, Delibašić B, Obradović, Z. Comprehensible predictive modeling using regularized logistic regression and comorbidity based features. *PloS one*, ISSN 1932-6203, 2015, vol. 10, no. 12, str. 1-6
11. Dinevski D, Povalej P, Kravos M. Intelligent data analysis for the diagnosis of alcohol dependence

syndrome. *Journal of international medical research*, ISSN 0300-0605, 2011, vol. 39, no. 3, str. 988-1000.
12. Povalej P, Gallego JA, Farina D, Holobar A. On repeatability of motor unit characterization in pathological tremor. V: International Conference on Neurorehabilitation, ICNR 2012, Toledo, Spain, November 14-16, 2012. PONS, José L. (ur.), TORRICELLI, Diego (ur.), PAJARO, Marta (ur.). *Converging clinical and engineering research on neurorehabilitation*, (Biosystems & Biorobotics, ISSN 2195-3562). Heidelberg [etc.]: Springer, cop. 2013, part 1, str. 553-556.
13. Fijačko N, Povalej P, Štiglic G. Mobile applications for type 2 diabetes risk estimation : a systematic review. *Journal of medical systems*, ISSN 1573-689X, oct. 2015, vol. 39, iss. 10,10str. http://link.springer.com/article/10.1007/s10916-015-0319-y/fulltext.html

1. Skelin M, Rupnik M, Volk M. Breeding of laboratory mice for biomedical research. Agricultura, ISSN 1580-8432. [Print ed.], 2010, issue 12, str. 33-40.
2. Skelin M, Rupnik M,, Cencič A. Pancreatic beta cell lines and their applications in diabetes mellitus research. Alternatives to animal experimentation, ISSN 1868-596X, 2010, letn. 27, št. 2, str. 105-113.
3. Dolenšek J, Rupnik M, Stožer A. Structural similarities and differences between the human and the mouse pancreas. Islets, ISSN 1938-2022, 2015, vol. 7, iss. 1, 16 str.
4. Stožer A, Dolenšek J, Skelin M, Rupnik M. Cell physiology in tissue slices : studying beta cells in the islets of Langerhans = Celična fiziologija v tkivnih rezinah : preučevanje celic beta v Langerhansovih otočkih. Acta medico-biotechnica, ISSN 1855-5640, 2013, vol. 6, [no.] 1, str. 20-32.
5. Stožer A, Dolenšek J, Rupnik M. Glucose-stimulated calcium dynamics in Islets of Langerhans in acute mouse pancreas tissue slices. PloS one, ISSN 1932-6203, 2013, vol. 8, iss. 1, str. 1-13, ilustr.
6. Dolenšek J, Skelin M, Rupnik M. Calcium dependencies of regulated exocytosis in different endocrine cells. Physiological research, ISSN 0862-8408, 2011, vol. 60, iss. Suppl. 1, str. S29-S38.
7. Skelin M, Dolenšek J, Stožer A, Rupnik M. Measuring exocytosis in endocrine tissue slices. V: THORN, Peter (ur.). Exocytosis methods, (Neuromethods, ISSN 0893-2336, Vol. 83). New York [etc.]: Springer, 2014, str. 127-146,
8. Dolenšek J, Stožer A, Skelin M, Miller E, Rupnik M. The relationship between membrane potential and calcium dynamics in glucose-stimulated beta cell syncytium in acute mouse pancreas tissue slices. PloS one, ISSN 1932-6203, 2013, vol. 8, iss. 12, str. 1-16.
9. Skelin M, Rupnik M. cAMP increases the sensitivity of exocytosis to Ca2+ primarily through protein kinase A in mouse pancreatic beta cells. Cell calcium, ISSN 0143-4160, 2011, vol. 49, issue 2, str. 89-99.
10. Jostins L, Mitrovič M, Potočnik U et.al. Host-microbe interactions have shaped the genetic architecture of inflammatorybowel disease. Nature (Lond.), 2012, vol. 491, no. 7422, str. 119-124, doi: 10.1038/nature11582.
11. Pinto Kozmus, C, Potočnik, U. Reference genes for real-time qPCR in leukocytes from asthmatic patients before and after anti-asthma treatment. Gene, ISSN 0378-1119.
12. Almouzni G, Grgurevič N, Majdič G, Potočnik U, Ilaš J, et al. Relationship between genome and epigenome - challenges and requirements for future research. BMC genomics, ISSN 1471-2164, 2014 Jun 18;15:487. doi: 10.1186/1471-2164-15-487. http://www.biomedcentral.com/1471-2164/15/487,
13. Berce V, Pinto Kozmus C, POTOČNIK, Uroš. Association among ORMDL3 gene expression, 17q21 polymorphism and response to treatment with inhaled corticosteroids in children with asthma. Pharmacogenomics journal, ISSN 1470-269X, Dec. 2013, vol. 13, issue 6, 523-529. http://www.nature.com/ tpj/journal/ vaop/ ncurrent/ full/tpj201236a.html
14. Mitrovič M, Potočnik U. High-resolution melting curve analysis for high-throughput genotyping of NOD2/CARD15 mutations and distribution of these mutations in Slovenian inflammatory bowel diseases patients. Dis Markers. 2011 Jan 1;30(5):265-74.