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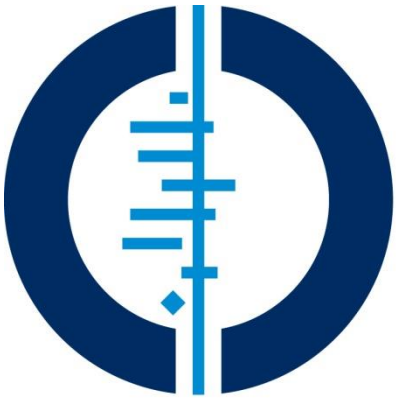
ABSTRACT BOOK



Cochrane Croatia

8th Croatian Cochrane Symposium
ABSTRACT BOOK

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Name of the presenting author is underlined

#1

Clinical trial transparency and data repositories; an environmental scan of the IMPACT (Improving Access to Clinical Trial Data) Observatory

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Background*:* The ongoing call for opening and reanalysis of clinical trial data is expected to contribute to higher reliability of evidence gained by systematic reviews and meta-analysis. Research data repositories (repositories) are digital repositories that store datasets and metadata on the Internet. They enable researchers to share data and are an essential role in increasing the accessibility and reusability of research data.

Objectives The objective of the IMPACT observatory is to identify and analyze characteristics of repositories that host clinical trial data, including barriers and gaps in data sharing practice. The findings will inform the scientific community at conferences, in publications, and by posting them on the Ottawagroup website.

Methods: Environmental scanning consists of collecting and analysing information about an environment, that can be used in planning and development. Our methodology included the identification of repositories that host clinical trial data and analysing their characteristics in Excel. We searched for repositories by reviewing R3data registry of research data repositories, Google search engine, and by direct communication. The information gathered from repositories' websites was complemented by contacting repositories managers.

Results: There is no clinical trial domain repository, but there are repositories that host any research data including clinical trial data. We identified and analyzed 11 such repositories in the public domain (Table 1). They are at international, national, or institutional levels. All repositories assign a unique identifier. However, there is no defined methodology or internationally accepted standard on how to prepare, post and access clinical trial data in the repository. Consequently, there is heterogeneity regarding uploading and access for reuse of data as well as of curatorship.

Conclusion: Repositories can play an important role in opening of clinical trial data by increasing the accessibility of data and facilitating its reuse. However a development of data sharing standards is essential.

Key words: clinical trials, repositories, data sharing and reuse

Table 1. Some characteristics of repositories in public domain that host clinical trial data as of April 2016

Name	Who can upload	Download access	Curated
B2SHARE	upon registration	uploader defined	self curate
BioGrid Australia Limited	upon project registration	upon approval	yes
Data Repository for the University of Minnesota	upon registration	open access	yes
DRYAD - Dryad Digital Repository	upon registration	open access	yes
EASY	upon registration	uploader defined	self curate
Edinburgh DataShare	upon registration	open access	self curate
Figshare	upon registration	open access	self curate
ICPSR - Inter-university Consortium for Political and Social	upon registration	uploader defined	self curate
Open Science Framework	upon registration	uploader defined	self curate
Research Data Australia	upon registration	uploader defined	depends on data and data scale
ZENODO	upon registration	uploader defined	yes

#2

Cochrane Plain Language Summaries and their adherence to standards

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Background: Cochrane systematic reviews have a plain language summary (PLS), which is aimed towards general public. PLSs should be clear, understandable, accessible and written in a standard format. Guidance for writing PLSs is specified in the Standards for the reporting of Plain Language Summaries in new Cochrane Intervention Reviews (PLEACS), but following these standards is currently not mandatory.

Objectives: To analyze adherence to the PLEACS of PLSs published after the publication of the latest version of PLEACS.

Methods: A systematic analysis of adherence to the measurable items of PLEACS was performed for Cochrane PLS published from March 2013 to the end of January 2015. Duplicate independent data extraction was performed. An adherence score was calculated for each PLS and for the Cochrane Review Groups (CRGs) that published them.

Results: Of the 1738 analyzed PLSs, not a single one adhered fully to the analyzed PLEACS items. The highest adherence was found for absence of complex statistical data (98% adherence), and the lowest adherence for an item mandating to address quality according to the GRADE system (0.7% adherence). Overall adherence percentage of PLSs reporting reviews with included studies was 57%. Different CRGs had a wide range of adherence scores.

Conclusion: Cochrane plain language summaries are highly heterogeneous with a low adherence to the PLEACS standards. A standardization of PLSs is necessary to ensure delivery of proper and consistent information for consumers and to facilitate knowledge translation. This is particularly important now when the PLSs are translated into 13 world languages.

Key words: plain language summary, adherence, quality standards

#3

Characteristics of clinical trials on drug-drug interaction registered in ClinicalTrials.gov from 2005 to 2015

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Background: Drug-drug interactions (DDIs) are one of the leading causes for market withdrawals and underlie 15-20% of adverse drug reactions requiring hospitalisation. Increasing numbers of chemical entities and more prevalent polypharmacy in ageing population emphasize the need for clinical studies of DDIs.

Objectives: To review the characteristics of clinical trials on DDIs in a publicly available trial register.

Methods: We performed a descriptive pilot study of clinical trials retrieved from the ClinicalTrials.gov by using the search term "drug-drug interaction" (search performed on October 16, 2005). Trials were included if they were 1) investigating the DDIs; 2) having a ClinicalTrials.gov registration number; 3) closed and completed in October 2015; 4) registered between June 23, 2005 and October 16, 2015. Data on 8 items from the World Health Organization Minimum Dataset[1] and on adverse events (AEs) were abstracted by one author and verified by another.

Results: Among 244 eligible trials, most were industry-sponsored (73%), started before registration (71%), and primarily interventional studies (97%). The majority of trials compared two interacting drugs (62%) and applied to healthy volunteers (78%). Pharmacokinetic parameters were primary outcome measures in 74% of trials. AEs were mostly included as secondary outcome measures (39 % vs. 5% as primary outcomes). Only a few studies (8%) had registered results, among which 16% reported serious and other AEs.

Conclusion: We found a remarkably low rate of reporting of study results and AEs, as well as inadequate time of registration. Further efforts to improve transparency are needed, such as enforcing regulatory requirements for timely and complete registration, and promoting it in existing regulatory guidance on drug interaction for industry.

Key words: characteristics, drug-drug interaction, ClinicalTrials.gov

Funding: Research Grant "Professionalism in Health" from the Croatian Science Foundation, No. IP-2014-09-7672

[1] World Health Organization. WHO Data Set. Geneva, Switzerland: World Health Organization; 2016. Available at http://www.who.int/ictrp/network/trds/en/. Accessed: April 20, 2016.

#4

Quality of evidence-based practice guidelines published in Croatia, 2004-2014: evaluation using the AGREE II tool

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Background and objective: We assessed the quality of guidelines published between 2004 and 2014 by the Croatian Medical Association.

Methods: Four independent raters assessed 51 guidelines from various clinical fields by using the validated AGREE II tool. The total score and the domain scores of AGREE scale were expressed as the percentage of maximum score.

Results: The raters scored consistently on AGREE II scale (average per-study interclass correlation coefficient = 0.82; range 0.60-0.91). Generally, the score was low, with the median total AGREE score of 35% (interquartile range, 29-43%). The domain "Rigour of Development", which assesses the evidence-based quality of recommendations, was among the worst rated (23%, interquartile range 16-34%). We did not observe any time-trend on domain scores, except for the increasing trend for the "Stakeholder Involvement" domain scores (trend-analysis, P=0.038). The composition of official bodies/type of developers constituting a guideline's working group clearly affected the end-quality of a guideline. National level guidelines supported by the Ministry of Health and unofficial working groups, regardless of the support from official professional societies, were the guidelines that constantly achieved highest scores throughout AGREE II domains. Moreover, the quality of guideline weakly decreased by the inclusion of greater number of official clinical societies in their development (Kendall's tau correlation from -0.229 to -0.278, P≤0.046 on two out of six AGREE domains and on the total score).

Conclusion: Guideline developers in Croatia should adopt better methodological framework in order to improve the quality of their clinical practice guidelines.

Key words: practice guidelines, quality assessment, AGREE-II, Croatia

Funding: Research Grant "Professionalism in Health" from the Croatian Science Foundation, No. IP-2014-09-7672

#5

Clinical trial data sharing in the 21st century: a scoping review of the literature, IMPACT (IMProving Access to Clinical Trial data) Observatory

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Background: There is increasing understanding of the importance of reanalysis of raw data for advancement of science, reducing research waste, and increasing the reliability of evidence gained by systematic reviews of clinical trials (CTs). The IMPACT Observatory is assessing transitions of CTs regarding data sharing.

Objectives: Present the preliminary results of a scoping review of the literature aiming to assess the dynamics of CT data transparency and related changes of culture, policies and practice since the baseline set in 2000.

Methods: A scoping review of the literature consists of a search, selection, and analysis of publications. Following independent analysis of the manual and PubMed search results two reviewers applied a consensus process to select papers that meet our criteria (Figure 1). Relevant information was extracted in Excel using predefined headings. Two reviewers coded and analyzed them and solved eventual disagreements by discussion.

Results: In the analysis of 132 selected papers we mapped the changes in CT data sharing since 2000. The focus of the scientific community evolved from publication bias over protocol disclosure to sharing of aggregate and raw data and forming databases and registries with open access. Data sharing, culture, guidelines, standards, policies, and databases are the main topics discussed (Figure 2)**.** The lack of methods and standards of data sharing are identified as the main gaps. Players include journal editors, publishers, researchers, funders, pharmaceutical industry, media, consumers, and regulators. Numerous events, including court cases, scandals, initiatives and projects influenced data sharing and CT enterprise.

Conclusion: Since the year 2000, we have witnessed important initiatives by numerous stakeholders aimed at improving the quality of evidence and reducing research waste by broader sharing and reuse of CT data. However, there are obstacles to overcome and gaps to fill including changing the research culture and developing methods and standards for data sharing.

Key words: transition in clinical trials, data sharing, initiatives, policy, evidence

Figure 1. Scoping review of literature, search, selection, extraction, and analysis; adapted Consort flow diagram

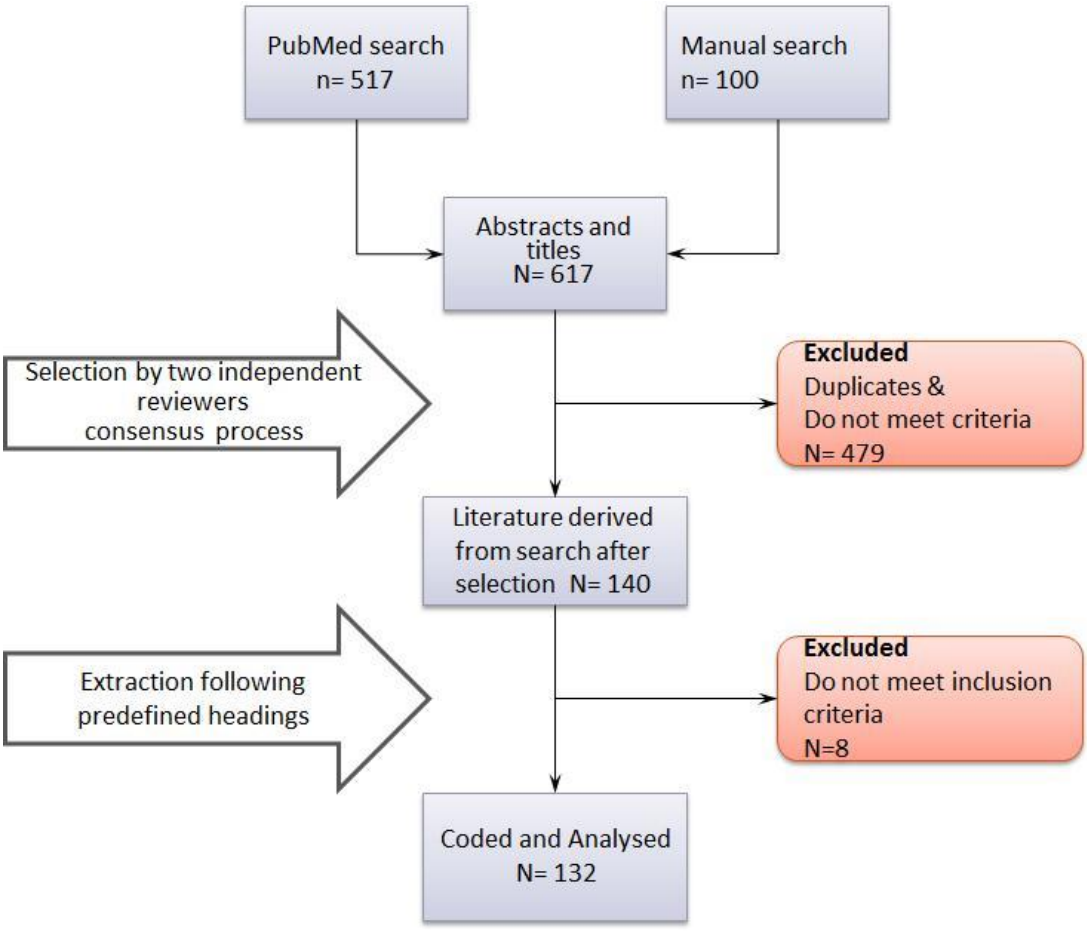
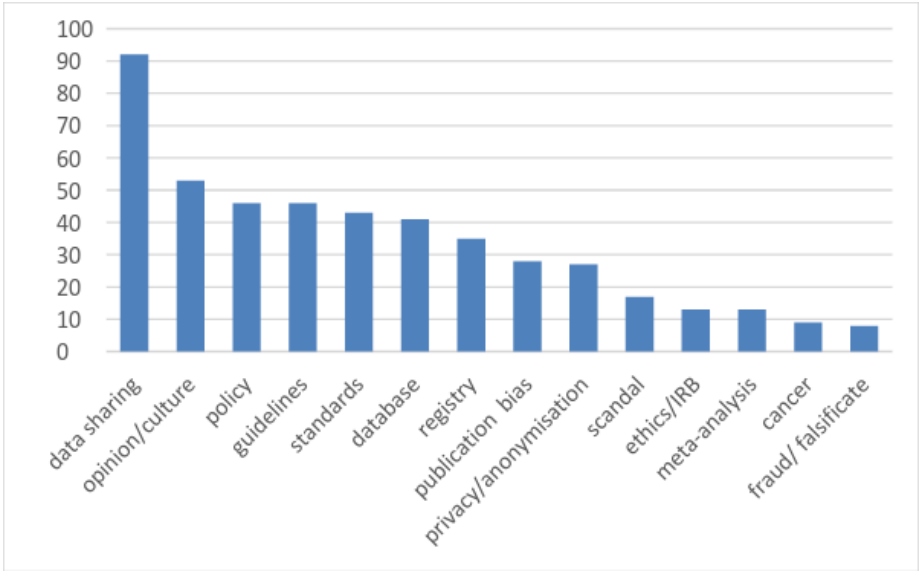


Figure 1. Frequency of topics discussed in the literature published since 2001; a scoping review of the literature on clinical trial data sharing; preliminary results



Note: Several topics can be discussed in the same paper

#6

Physicians' awareness of Cochrane in a canton of a middle income country (Bosnia and Herzegovina)

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Background: Cochrane Library (CL) is the only evidence based medicine (EBM) database available in Bosnia and Herzegovina (BH) with unrestricted access. Zenica-Doboj Canton (ZDC) is a typical, average BH canton, located in the heart of BH.

Objectives: In this study we aimed to assess knowledge, attitude and usage of CL among physicians in ZDC, in order to help in the implementation of educational activities that would improve the use of EBM and the CL.

Methods: Anonymous questionnaire and an explanatory letter were sent by post to all physicians working in all state owned health institutions (2 hospitals and 11 Primary Health Care Institutions) in ZDC. The response rate was 64 % (358 of 559 physicians).

Results: 124 (34.64%) of respondents heard about Cochrane and 117 (33%) heard about CL. The information was obtained mostly on the internet and from colleagues. 69 (19%) physicians used CL. 18 (5%) read full articles. Most access to CL was achieved from home – 42 (12%) respondents, and 24 (7%) respondents used it several times a month. Respondents considered in 41 cases (11%) that CL helped enough. There were 67 (19%) physicians willing to learn more about the methodology of performing Cochrane systematic reviews.

Conclusion: The awareness on CL in ZDC was not very high, but the attitudes toward CL were positive. There is a need for specially designed educational interventions that would encourage physicians to use CL.

Key words: awareness, physicians, Cochrane

#7

Cochrane Systematic Reviews as a tool for decisions on drugs reimbursement in a decentralized decision-making environment

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Background: Not all drugs are the same, neither regarding efficacy, nor regarding safety, eg. some should be given higher priority in reimbursement. Cochrane systematic reviews (CSRs) represent unbiased evidence, highest in hierarchy. Bosnia and Herzegovina is highly decentralized environment regarding decision-making in health, since there are 14 funds that decide on reimbursement.

Objectives: To test CSRs as additional tool for decision making in drug reimbursement for drugs that are on the core national reimbursement list of Federation of Bosnia and Herzegovina (FBL) but not on the 18th World Health Organization Essential Medicines List (WHO EML).

Methods: Cochrane Summaries were searched using the search strategy which included the generic name of the targeted medicine in title, abstract and keywords. The full text of the most recent update of the retrieved CSR was analysed. When the CSR reported same or more benefits as other medicines, same or more benefits as other medicines but substantial side effects, or overview we considered this as good evidence to justify inclusion. The findings of ineffective or fewer benefits than other medicines or and less effective than alternatives, more side effects were considered as good evidence to justify exclusion. This categorisation was performed by one author, and any uncertainty was discussed with the other author to reach a consensus.

Results: Out of 124 medicines on FBLs but not on EML, 52 (42%) had good CSR evidence supporting their inclusion (n=38) or exclusion (n=13). The largest amount of favourable evidence was found for cancer medicines (18 out of 38, 47%). For 86 medicines (69%), we could not find sufficient evidence supported by CSRs to recommend their use for various reasons.

Conclusion: CSRs are unbiased evidence of highest quality that can supplement WHO EML in making decisions on reimbursement in a decentralized environment.

Key words: Cochrane systematic reviews, drugs, reimbursement

#8
Reporting of clinical trials results registered in ClinicalTrials.gov and peer-reviewed journals

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Objective: To assess the effectiveness of legislative initiatives to stimulate public registration of trial results, we assessed adherence to protocol and results reporting, changes to registry and publication data for randomized clinical trials (RCT) after introduction of Food and Drug Administration Amendments Act (FDAAA).

Study Design and Setting: Observational study of a cohort of ClinicalTrials.gov registered FDAAA-covered RCTs found through ClinicalTrials.gov between 2009 and 2012.
Methods: We extracted World Health Organization Minimum Data Set[2] items and study characteristics from ClinicalTrials.gov from the initial to last registration and from corresponding publications. We assessed discrepancies between the two data sources. Data were abstracted by one and verified by another author.

Results: Among 81 eligible trials, most were industry-funded, with a drug intervention in parallel assignment. Secondary outcomes at initial and last registration were omitted for 17% and 20% of RCTs, respectively. RCT registration changes mostly involved scientific title (19%). Inclusion criteria omission was most common (88%) in publications. Inferential statistical methods for primary and secondary outcomes matched between registry and publication for 53% and 29% of RCTs, respectively. Serious and other adverse events that were absent for 24% and 4.8% of RCTs, respectively, were published as non-occurring.

Conclusion: Discrepancies remain relatively high between registered and published outcomes, particularly regarding registered omissions in publications and concomitant reporting, nature of statistical method used, and reporting of adverse events. This seriously undermines transparency surrounding clinical trials and their results. Stakeholders, administrators, and regulatory officials in health research need to focus on improving data reporting from clinical trials.

Key words: randomized controlled trials as topic, databases factual, drug side effects

[2] World Health Organization. WHO Data Set. Geneva, Switzerland: World Health Organization; 2016: Available at http://www.who.int/ictrp/network/trds/en/. Accessed April 21, 2016.

#9

Use of medical terminologies to describe adverse event terms in ClinicalTrials.gov

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Objective: To describe the type of medical terminology used and variability of adverse event terms in ClinicalTrials.gov in context of mandates by the Food and Drug Administration Amendments Act of 1997 to promote transparency surrounding reporting of trial data.

Study Design and Setting: Cross-sectional study on safety and efficacy trials in ClinicalTrials.gov for common drug classes: antidepressants, analgesics or anesthetics, antidepressants, anti-allergics, anti-infectives, enzyme inhibitors, and anti-inflammatory, antineoplastic, hypoglycemic, neuromuscular agents.

Methods: Registered and completed clinical trials with adverse events between 2009 and 2012. We identified trials that studied the 10 drug categories from safety and efficacy trials. We excluded trials without a drug intervention or adverse events.

Results: Out of 93 trials that studied drugs, pain was most studied (n = 5, 5.4%), followed by major depressive disorder and acne vulgaris, (both n = 4, 4.3%). Most trials were randomized (n = 63, 67.7%). MedDRA was the most commonly used (n = 30, 32.3% and n = 45, 48.44%) dictionary for serious and other adverse events (SAEs and OAEs), respectively. Predominantly, 67 (72%) trials reported OAEs, whereas 42 (45.2%) reported SAEs. Majority (n = 51, 54.8%) of drugs were an FDA indication. Omitted medical terminology sources were 10 (10.8%) for trials with SAEs and 18 (19.4%) for OAEs. Of 236 lay terms for both SAEs and OAEs, the same lay term defined up to 3 different adverse events in 11 (11.8%) and 69 (74.2%) trials, respectively.

Conclusion: MedDRA was predominantly used to define adverse events from safety and efficacy drug trials. Variation in the use of multiple terms to convey the same adverse event term was minimal. However, many studies failed to provide a source dictionary. Without a standardized dictionary or version required by ClinicalTrials.gov, there may be a reduction in the comparability of adverse events across studies. Administrators at ClinicalTrials.gov may consider the peremptory use of MedDRA or lay terms.

Key words: side effects, clinical trial, data bases, biomedical ontologies

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#10

Are Croatian patients aware of clinical trials?

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Background: There is a constant increase in new clinical trials, but patients often remain uninformed of their existence, especially if they do not have access to adequate information about clinical research.

Objectives: To assess how informed Croatian patients are about clinical trials.

Methods: We performed a survey study on a convenience sample of 257 patients visiting two family medicine offices, patients from the Department of Oncology of the University of Split Hospital Centre, members of patients' associations, and patients answering a web-survey publicized online. The survey responses were collected in a 2-month period in 2015. The survey was voluntary and anonymous, and was approved by the Ethics Committee of the University of Split School of Medicine.

Results: Survey respondents were mostly 41 to 80 years old (67%), and 53% were women. 21% were members of patients' associations. Although 66% of the respondents were aware of clinical trials, only 15% were informed about possibilities of participating in a trial. Furthermore, although 58% of the respondents were willing to try new treatments, only 6% actually participated in a clinical trial. Men significantly more often reported being informed about clinical trials than women (63% vs. 37%, P=0.021). Although they reported that they can talk to physicians about their disease, a half of the respondents searched for more information, mostly from friends (33%) or on the Internet (41%) mostly using general internet searches rather than specialized health sites. Only 2% of the respondents were aware of publicly available trial registries, such as ClinicalTrials.gov. Respondents who were members of patients' associations were more likely to report being informed about clinical trial and to actually participate in a trial.

Conclusions: The awareness of Croatian patients about clinical trials and the possibilities of participating in them is rather low, despite reported availability of Internet access and good communication with their physicians. There is a need for active public health measures to increase the awareness of and access to clinical trials to patients in Croatia.

Key words: clinical trials, clinical research, patient awareness

Funding: Research Grant "Professionalism in Health" from the Croatian Science Foundation, No. IP-2014-09-7672