KREP

2025

KARNATAKA RADIOLOGY EDUCATION PROGRAM

CLINICAL RESEARCH – BRIDGING IMAGING & INNOVATION

SESSION -1- INTRODUCTION TO CLINICAL RESEARCH

DR MUNIRAJU MARALAKUNTE

MBBS, MDRD (PGIMER), MBA (HHSM, BITS-PILANI)

REVIEWER-BMJ CASE REPORTS

ASSISTANT PROFESSOR

DEPTT. OF RADIOLOGY

SMSIMSR, CHIKKABALLAPUR

DEFINITION & SCOPE OF MEDICAL RESEARCH

- ✓ TO BE DONE ON HUMAN BEINGS
- ✓ INTENDED TO PRODUCE KNOWLEDGE FOR UNDERSTANDING DISEASE, PROMOTION/PREVENTION/TREATING/PALLIATION OF ILLNESS
- ✓ EXPLORES
  - ETIOPATHOGENESIS
  - TRANSLATIONAL RESEARCH
  - NATURAL HISTORY, CLINICAL DATA, DETECTION & DIAGNOSIS
  - THERAPEUTIC – DRUGS, DEVICES, INSTRUMENTS, BIOLOGICS
  - BEHAVIOURAL RESEARCH
  - HEALTH SERVICES
  - COMMUNITY BASED RESEARCH

WHY IS CLINICAL RESEARCH REQUIRED?

- ✓ CRUCIAL IN ADVANCING MEDICAL KNOWLEDGE
- ✓ SYSTEMATIC STUDY OF HEALTH & ILLNESSES
- ✓ TO KNOW, AND IMPROVE THE DIAGNOSTIC ACCURACY OF IMAGING OR OTHER TESTS
- ✓ IDENTIFICATION OF EFFECTIVE THERAPIES WHICH ENHANCE OVERALL QUALITY AND LONGEVITY OF HUMAN LIFE
- ✓ CLINICAL TRIALS RIGOROUSLY TEST THE SAFETY & EFFICACY OF NEW MEDICAL INTERVENTIONS
- ✓ TO REDISTRIBUTE THE HEALTH RESOURCES
- ✓ TO PRACTICE EVIDENCE BASED MEDICINE

TYPES OF CLINICAL RESEARCH

BASED ON RESEARCHER'S BEHAVIOUR – OBSERVATIONAL STUDY

COLLECTION, ANALYSIS & INTERPRETATION OF THE MEDICAL DATA ONLY

Original Article

Prevalence of Osteoporosis and Sarcopenia in Middle-Aged Subjects with Low Back Pain

Shamrendra Narayan , Rishabh Pratap , Gaurav Raj , Abhishek Chauhan , Tushant Kumar , Neha Singh , Ajai Kumar Singh , Nikhil Gupta

Abstract

Objective The genesis of both osteoporosis and sarcopenia is multifactorial, complicated, and interrelated. The present study has been undertaken to analyze the prevalence of low bone mineral density (BMD) and the pattern of imaging markers of sarcopenia (paraspinal skeletal muscle area [SMA] and skeletal muscle index [SMI] with respect to clinicodemographic profile in middle-aged patients (30–45 years) undergoing evaluation for low back pain (LBP).

Materials and Methods Magnetic resonance imaging (MRI) of the lumbosacral spine and/or sacroiliac joints was done on 3T MRI. BMD of the lumbar spine (L1 to L4) was assessed using a dual-energy X-ray absorptiometry scan. SMA was calculated by measuring the cross-sectional area of paraspinal muscles (bilateral psoas, erector spinae, and multifidus), and SMI was calculated by dividing SMA by height^2.

Results The prevalence of osteoporosis was 12.1% in patients of age 30 to 45 years presenting with LBP. Both osteoporosis and paraspinal muscle mass were statistically associated with the duration of symptoms (p-value <0.05). No statistically significant difference was observed in different MRI findings, that is, normal, inflammatory, infective, and degenerative etiology.

Conclusion Low BMD and loss of muscle mass in cases with LBP are more related to duration of disease rather than etiology or gender in middle-aged subjects. Early intervention to manage LBP may prevent progression to osteoporosis and sarcopenia in young adults.

TYPES OF CLINICAL RESEARCH

BASED ON RESEARCHER'S BEHAVIOUR – EXPERIMENTAL STUDY

INTERVENTION IS A MUST FOR THE STUDY

Efficacy of Ultrasound-Guided Injection of Platelet-Rich Plasma in Treatment of Sports-Related Meniscal Injuries

Prabakar Singh Raju , Makesh Ram Sriraghavan , Pazhani Jayaraman , Bheeshma Balasubramaniam , Karthik Shanmugavel Karuppiah , Poornima Kumararaja

Abstract

Purpose Meniscal injuries are a common occurrence in sports-related activities, often leading to pain, reduced joint function, and impaired athletic performance. This study aimed to evaluate the role of ultrasound-guided intra-articular platelet-rich plasma (PRP)-rich fluid injection which was obtained through serial centrifugation in the treatment of meniscal injuries resulting from sports activities.

Materials and Methods A prospective study was conducted involving 54 cases with grade I, II, and III meniscal injuries, aged 18 and 43 years. PRP-rich fluid was prepared by subjecting autologous blood samples to a two-step centrifugation process. Patients were assessed pretreatment and at regular intervals posttreatment.

Results Patients reported reduced pain and improved joint functionality following treatment. Average age of the patients was 34.4 years, and average follow-up period was 275.1 days. It is noteworthy that no cases of bilateral meniscal injuries were identified; indicating that the focus was primarily on single knee injuries. Predominance of grade II injuries suggests that the PRP intervention might be particularly effective in addressing more severe meniscal tears.

Conclusion The results of our study provide compelling evidence for the positive impact of PRP augmentation in meniscus repair. Our findings indicate that PRP therapy has the potential to bring about substantial benefits for individuals with meniscus tears of the knee, particularly in terms of pain relief and enhanced functional capabilities.

TYPES OF CLINICAL RESEARCH

BASED ON PURPOSE – SCREENING TRIALS

Clinical Trial > J Natl Cancer Inst Monogr. 1997:(22):37-41. doi: 10.1093/jncimono/1997.22.37.

The Canadian National Breast Screening Study: update on breast cancer mortality

A B Miller [1], T To, C J Baines, C Wall

Affiliations + expand

PMID: 9709273 DOI: 10.1093/jncimono/1997.22.37

Abstract

The Canadian National Breast Screening Study (CNBSS), conducted on women age 40-49, was designed to evaluate the efficacy of combined annual mammography and physical examination of the breasts in reducing breast cancer mortality in comparison to usual care (UC) controls. From January 1980 through March 1985, 25,214 women were individually randomized to the mammography/physical exam (MP) arm and 25,216 to the UC. The integrity of the randomization has been reviewed and confirmed to be unbiased. During an average, follow-up of 10.5 years from entry (range: 8.75-13 years), 82 women died from breast cancer in the MP arm and 72 in the UC, for a rate ratio of 1.14 (95% confidence interval: 0.83-1.56). All-cause mortality was almost identical comparing the two groups; the nonsignificant excess of breast cancer deaths in the MP arm was balanced by an excess of other cancer deaths in the UC arm.

TYPES OF CLINICAL RESEARCH

BASED ON PURPOSE – PREVENTION TRIALS

A randomized trial of effects of health risk appraisal combined with group sessions or home visits on preventive behaviors in older adults

Abstract

Background: To explore effects of a health risk appraisal for older people (HRA-O) program with reinforcement, we conducted a randomized controlled trial in 21 general practices in Hamburg, Germany.

Methods: Overall, 2,580 older patients of 14 general practitioners trained in reinforcing recommendations related to HRA-O-identified risk factors were randomized into intervention (n = 878) and control (n = 1,702) groups. Patients (n = 746) of seven additional matched general practitioners who did not receive this training served as a comparison group. Patients allocated to the intervention group, and their general practitioners, received computer-tailored written recommendations, and patients were offered the choice between interdisciplinary group sessions (geriatrician, physiotherapist, social worker, and nutritionist) and home visits (nurse).

Results: Among the intervention group, 580 (66%) persons made use of personal reinforcement (group sessions: 503 [87%], home visits: 77 [13%]). At 1-year follow-up, persons in the intervention group had higher use of preventive services (eg, influenza vaccinations, adjusted odds ratio 1.7; 95% confidence interval 1.4-2.1) and more favorable health behavior (eg, high fruit/fiber intake, odds ratio 2.0; 95% confidence interval 1.6-2.6), as compared with controls. Comparisons between intervention and comparison group data revealed similar effects, suggesting that physician training alone had no effect. Subgroup analyses indicated favorable effects for HRA-O with personal reinforcement, but not for HRA-O without reinforcement.

Conclusions: HRA-O combined with physician training and personal reinforcement had favorable effects on preventive care use and health behavior.

TYPES OF CLINICAL RESEARCH

BASED ON PURPOSE – DIAGNOSTIC TRIALS

Comparison of Dual-Energy Computed Tomography Pulmonary Angiography-Derived Contrast Enhancement with Standard Dual-Energy Pulmonary Angiography in Diagnosing Subsegmental Pulmonary Embolism: A Prospective Study

Vivek Yadav[1,#] Manphool Singhal[1,#] Muniraju Maralakunte[1] Navneet Sharma[2] Arun Sharma[1] Anupam Lal[1]

Objective In this study, we compare the diagnostic accuracy of dual-energy (DE) computed tomography pulmonary angiography (CTPA) derived contrast enhancement (DECTPA, CTPA images with iodine maps) with standard dual-energy pulmonary angiography (SCTPA) for diagnosis of subsegmental pulmonary embolism in the cases with clinical suspicion of acute pulmonary embolism (APE).

Materials and Methods We included 50 cases with clinical suspicion of APE that were referred for CTPA. All the patients underwent CTPA in the dual-energy protocol. Two radiologists evaluated the images. The first radiologist interpreted the SCTPA images (vascular images) and the second radiologist interpreted the DECTPA (CTPA images with iodine maps) for findings of APE. We calculated the sensitivity, specificity, and negative predictive value of DECTPA vis-à-vis SCTPA images.

Results The DECTPA with the advantage of iodine map utilization yielded higher detection of thrombi in peripheral subsegmental arteries (72 vs. 99; $p = -0.001$) as compared to the SCTPA images by identification of 18 new perfusion defects (interquartile range [IQR]: 0–1) that were consistent with APE. Filling defects were identified in 27 (IQR: 0–4) more subsegmental arteries supplying these 18 areas, which were not detected on SCTPA alone. These 18 perfusion defects were identified in 13 cases. In these 13 cases, 4 new cases were diagnosed that were negative on CTPA ($p = -0.125$).

In the evaluation of the APE, sensitivity and specificity were calculated and it was found that DECTPA showed 100% sensitivity and 86% specificity with 100% negative predictive value in the detection of thrombi as compared to the routine CTPA.

TYPES OF CLINICAL RESEARCH

BASED ON PURPOSE – TREATMENT TRIALS

Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma

Christian U Blank [1], Minke W Lucas [1], Richard A Scolyer [1], Bart A van de Wiel [1], Alexander M Menzies [1], Marta Lopez-Yurda [1], Lotte L Hoeijmakers [1], Robyn P M Saw [1], Judith M Lijnsvelt [1], Nigel G Maher [1], Saskia M Pulleman [1], Maria Gonzalez [1], Alejandro Torres Acosta [1], Winan J van Houdt [1], Serigne N Lo [1], Anke M J Kuijpers [1], Andrew Spillane [1], W Martin C Klop [1], Thomas E Pennington [1], Charlotte L Zuur [1], Kerwin F Shannon [1], Beatrijs A Seinstra [1], Robert V Rawson [1], John B A G Haanen [1], Sydney Ch'ng [1], Kishan A T Naipal [1], Jonathan Stretch [1], Johannes V van Thienen [1], Michael A Rtshiladze [1], Sofie Wilgenhof [1], Rony Kapoor [1], Aafke Meerveld-Eggink [1], Lindsay G Grijpink-Ongering [1], Alexander C J van Akkooi [1], Irene L M Reijers [1], David E Gyorki [1], Dirk J Grünhagen [1], Frank M Speetjens [1], Sonja B Vliek [1], Joanna Placzke [1], Lavinia Spain [1], Robert C Stassen [1], Mona Amini-Adle [1], Céleste Lebbé [1], Mark B Faries [1], Caroline Robert [1], Paolo A Ascierto [1], Rozemarijn van Rijn [1], Franchette W P J van den Berkmortel [1], Djura Piersma [1], Andre van der Westhuizen [1], Gerard Vreugdenhil [1], Maureen J B Aarts [1], Marion A M Stevense-den Boer [1], Victoria Atkinson [1], Muhammad Khattak [1], Miles C Andrews [1], Alfons J M van den Eertwegh [1], Marye J Boers-Sonderen [1], Geke A P Hospers [1], Matteo S Carlino [1], Jan-Willem B de Groot [1], Ellen Kapiteijn [1], Karijn P M Suijkerbuijk [1], Piotr Rutkowski [1], Shahneen Sandhu [1], Astrid A M van der Veldt [1], Georgina V Long [1]

Affiliations + expand

PMID: 38828984 DOI: 10.1056/NEJMoa2402604

Background: In phase 1-2 trials in patients with resectable, macroscopic stage III melanoma, neoadjuvant immunotherapy was more efficacious than adjuvant immunotherapy.

Methods: In this phase 3 trial, we randomly assigned patients with resectable, macroscopic stage III melanoma to two cycles of neoadjuvant ipilimumab plus nivolumab followed by surgery or surgery followed by 12 cycles of adjuvant nivolumab. Only patients in the neoadjuvant group with a partial response or nonresponse received adjuvant treatment. The primary end point was event-free survival.

Results: A total of 423 patients underwent randomization. At a median follow-up of 9.9 months, the estimated 12-month event-free survival was 83.7% (99.9% confidence interval [CI], 73.8 to 94.8) in the neoadjuvant group and 57.2% (99.9% CI, 45.1 to 72.7) in the adjuvant group. The difference in restricted mean survival time was 8.00 months (99.9% CI, 4.94 to 11.05; P<0.001; hazard ratio for progression, recurrence, or death, 0.32; 99.9% CI, 0.15 to 0.66). In the neoadjuvant group, 59.0% of patients had a major pathological response, 8.0% had a partial response, 26.4% had a nonresponse (>50% residual viable tumor), and 2.4% had progression; in 4.2%, surgery had not yet been performed or was omitted. The estimated 12-month recurrence-free survival was 95.1% in patients in the neoadjuvant group who had a major pathological response, 76.1% among those with a partial response, and 57.0% among those with a nonresponse. Adverse events of grade 3 or higher that were related to systemic treatment occurred in 29.7% of patients in the neoadjuvant group and in 14.7% in the adjuvant group.

Conclusions: Among patients with resectable, macroscopic stage III melanoma, neoadjuvant ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy resulted in longer event-free survival than surgery followed by adjuvant nivolumab. (Funded by Bristol Myers Squibb and others; NADINA ClinicalTrials.gov number, NCT04949113.).

TYPES OF CLINICAL RESEARCH

BASED ON PURPOSE – QUALITY OF LIFE TRIALS

Clinical Trial > J Clin Oncol. 1992 Dec;10(12):1833-8. doi: 10.1200/JCO.1992.10.12.1833.

Prognostic value of quality-of-life scores during chemotherapy for advanced breast cancer. Australian New Zealand Breast Cancer Trials Group

A Coates [1], V Gebski, D Signorini, P Murray, D McNeil, M Byrne, J F Forbes

Affiliations + expand

PMID: 1453197 DOI: 10.1200/JCO.1992.10.12.1833

Abstract

Purpose: We observed that quality-of-life (QL) scores, collected to evaluate treatment in a randomized trial in advanced breast cancer, predicted survival duration. This report explores the prognostic associations between QL and survival in more detail.

Patients and methods: In a randomized clinical trial comparing intermittent and continuous therapy policies for patients with advanced breast cancer, QL was measured by linear analog self-assessment (LASA) and the Quality-of-Life Index (QLI). Baseline scores and subsequent changes were included in statistical models of survival duration, with and without other prognostic factors.

Results: Physician assessment of QLI and patient LASA scores for physical well-being (PWB), mood, nausea and vomiting, appetite, and overall QL (but not pain) at the commencement of treatment were significant predictors of subsequent survival. Scores for PWB and QLI were independent of other prognostic factors. Changes in scores were also prognostically important. Both baseline and change in scores for PWB, mood, pain, and QLI after the first three treatment cycles, but before an arbitrary 180-day time point, were significantly predictive of survival beyond that time. Both QLI and PWB were prognostically independent of tumor response. Although QL improvement was correlated with tumor response, continuous therapy yielded significantly better QL scores, even in nonresponders.

Conclusion: These findings support the validity of the simple QL measures used in the trial. They are compatible with the simple explanation that patients perceive disease progression before it is clinically evident, but also with a causal relationship between QL and survival duration.

TYPES OF CLINICAL RESEARCH

BASED ON PURPOSE – COMPASSIONATE TRIALS (ON NON-TREATABLE PATIENT SUBGROUP)

Article | Published: 22 May 2024

Cadonilimab with chemotherapy in HER2-negative gastric or gastroesophageal junction adenocarcinoma: the phase 1b/2 COMPASSION-04 trial

Xiangyu Gao, Ke Ji, Yongning Jia, Fei Shan, Ye Chen, Nong Xu, Ziyu Jia, Tianshu Liu, Nong Yang, Haijun Zhong, Changzheng Li, Zengqing Guo, Qingxia Fan, Xiaoyan Lin, Yan Zhang, Hui Ren, Hongxia Yang, Zhifang Yao, Wei Liu, Zhongmin Maxwell Wang, Baiyong Li, Michelle Xia, Lin Shen ✉, Ziyu Li ✉ & Jiafu Ji

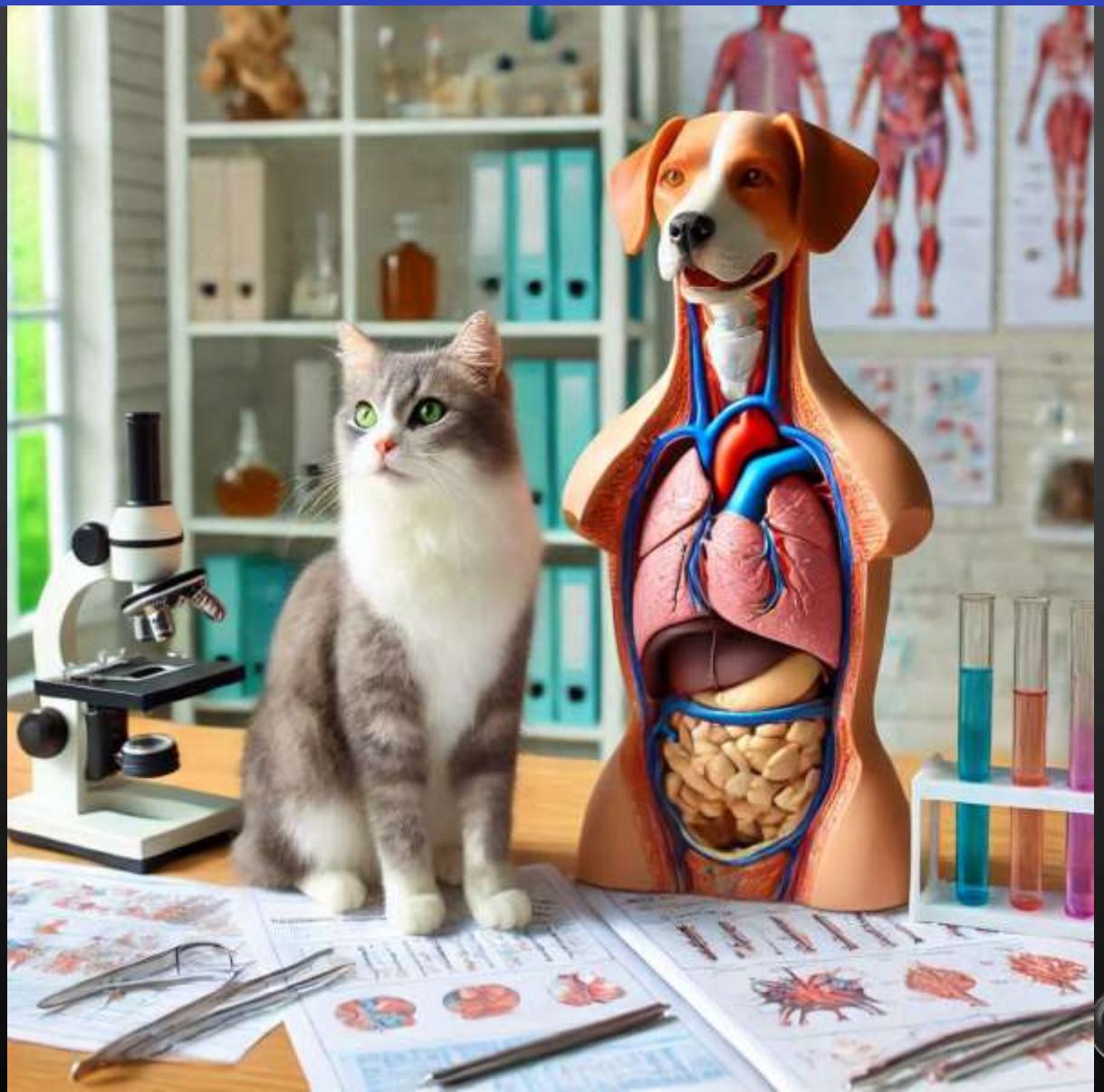
Abstract

Treatment with anti-programmed cell death protein 1 (PD-1) therapy and chemotherapy prolongs the survival of patients with unresectable advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. The benefit from anti-PD-1 therapy is enriched in patients with programmed cell death 1 ligand 1 (PD-L1) combined positive score (CPS)-positive or CPS-high tumors compared with patients with PD-L1 CPS-negative or CPS-low tumors. In this phase 1b/2 study, we evaluated the efficacy and safety of cadonilimab, a bispecific antibody targeting PD-1 and cytotoxic T-lymphocyte antigen-4, plus chemotherapy as first-line treatment in patients with human epidermal growth factor receptor 2-negative unresectable advanced or metastatic gastric or GEJ adenocarcinoma. The primary endpoint was the recommended phase 2 dose (RP2D) for phase 1b and the objective response rate for phase 2. Secondary endpoints included disease control rate, duration of response, time to response, progression-free survival, overall survival (OS) and safety. The primary endpoint was met. No dose-limiting toxicities were observed during dose escalation in phase 1b; the recommended phase 2 dose was determined as 6 mg kg^{-1} every 2 weeks. The objective response rate was 52.1% (95% confidence interval (CI) = 41.6–62.5), consisting of complete and partial responses in 4.3% and 47.9% of patients, respectively. The median duration of response, progression-free survival and OS were 13.73 months (95% CI = 7.79–19.12), 8.18 months (95% CI = 6.67–10.48) and 17.48 months (95% CI = 12.35–26.55), respectively. The median OS in patients with a PD-L1 CPS ≥ 5 was 20.32 months (95% CI = 4.67–not estimable); in patients with a PD-L1 CPS < 1, the median OS reached 17.64 months (95% CI = 11.63–31.70). The

PHASES OF CLINICAL TRIALS

Phase	Purpose	Participants	Duration
Phase 0	Exploratory studies with very small doses to gather preliminary data	Fewer than 15 people	Several months
Phase I	Assess safety, dosage range, and side effects	20-100 healthy volunteers or patients	Several months
Phase II	Evaluate effectiveness and further assess safety	100-300 patients	Several months to 2 years
Phase III	Confirm effectiveness, monitor side effects, compare to standard treatment, and collect additional information	300-3,000 patients	1-4 years
Phase IV	Post-marketing studies to gather additional information on long-term effectiveness and side effects	Various	Ongoing

QUIZ – CAN YOU CALL A STUDY ON ANIMALS (WITH DRUGS/ BEHAVIOUR PARADIGMS) AS CLINICAL RESEARCH?



ANSWER – NO. IT IS CALLED AS PRECLINICAL PHASE OF TRIAL.

THANK YOU