Protokol kliničnega preskušanja

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Klinična preskušanja

datum seje	EudraCT števil	protokol	faza	sponzor	preskuševalec
23. 2. 10	2009-017659-83		IV	BGP KRANJ	Bolnišnica Kranj
23. 2. 10	2009-016752-52		IV	BGP KRANJ	Bolnišnica Kranj
23. 2. 10	2009-015532-14	EMR700692-003	II	Merck	UKC LJ
23. 2. 10	2006-003173-27	20060163	III	Amgen	SB Slovenj Gradec
23. 2. 10	2009-014377-40	BAY 58-2667/14560	IIb	Bayer HealthCare	UKC LJ
23. 2. 10	2007-005792-34	20070782	III	Amgen	Bolnišnica Golnik
20. 4. 10	2010-018838-45	RLY5016-204	IIb	Relypsa, Inc. ZDA	Bolnišnica Golnik
20. 4. 10	2009-017622-39	ERNLO01	IV	UKC LJ	UKC KO za kardiologijo
20. 4. 10	2009-017745-55	205.424	II	Boehringer Ingelheim Avstrija	alergološka amb Mb, s.p.
20. 4. 10	2009-018054-33	09-001	IV	Fakulteta za farmacijo	Psihiatrična klinika
20. 4. 10	2009-015556-15	101MS325	IIIb	biogen IDEC	UKC LJ NEVROLOŠKA
6. 7. 10	2009-017775-19	CAMN107EIC01	IIIb	Novartis Švica	UKC LJ HEMATOLOŠKA
6. 7. 10	2010-019374-32	CP-4-003	II	Modigenetech Izrael	UKC LJ DIABETOLOŠKA
6. 7. 10	2009-016826-15	CECOG/BC1.2.001	II	CECOG	Onkološki inštitut
6. 7. 10	2009-017095-24	ARETA, AOP13007	III	AOP Orphan Pharmac	UKC LJ HEMATOLOŠKA
6. 7. 10	2010-019094-15	DSC/08/2357/36	II	Italfarmaco	UKC LJ PEDIATRIČNA
6. 7. 10	2009-011299-32	20060359	III	Amgen, ZDA	UKC MB Ginekologija
6. 7. 10	2009-016258-41	1245.23	III	Boehringer Ingelheim Avstrija	Šubic Diabetologija d.o.o.
7. 9. 10	2009-014894-42	NN304-3785	IV	Novo Nordisk	SB Novo mesto
7. 9. 10	2009-015247-16	MK-0653C-162	III	MSD	Bolnišnica Golnik
7. 9. 10	2010-018974-19	ANA-3786	IV	Novo Nordisk	SB Novo mesto
7. 9. 10	2007-001370-88	IBCSG-35-07, BIG-1-07-SOLE	III	IBCSG	Onkološki inštitut
7. 9. 10	2010-022172-30		IV	Fakulteta za farmacijo	UKC LJ KIRURŠKA
20. 10. 10	2010-021057-39	NN2211-1800	I	Novo Nordisk	UKC LJ PEDIATRIČNA
20. 10. 10	2008-006180-36	22071-24071	III	EORTC	Onkološki inštitut
20. 10. 10	2010-023362-44	ITAC 2	II	projekt-ministrstvo za visoko šolstvo	Onkološki inštitut
15. 12. 10	2010-019821-32	20090508	III	Amgen ZDA	Onkološki inštitut
15. 12. 10	2009-012576-27	SORAMIC	II	University Hospital Magdeburg	UKC LJ RADIOLOGIJA
15. 12. 10	2006-005951-14		IV	AIFA	UKC LJ DIABETOLOŠKA

Klinično preskušanje zdravil - NAČELA

- znanstveno utemeljeno preskušanje
- preskušanje vodeno po etičnih načelih
- pravice, varnost in dobrobit preizkušanca prednostni pred interesi znanosti in družbe
- pričakovane koristi pri zdravljenju bolnikov večje od predvidenega tveganja
- verodostojnost podatkov o kliničnem preskušanju
- zaupnost podatkov preizkušancev
- ustrezna izobrazba, izkušnje in strokovna usposobljenost sodelujočih v kliničnem preskušanju

Dobra klinična praksa

Zakon o zdravilih (UL 31/2006):

- mednarodni etični in znanstveni sistem kakovosti
- nanaša se na načrtovanje, izvajanje, zapisovanje, nadzorovanje in poročanje o kliničnem preskušanju na ljudeh
- zagotavlja verodostojnost podatkov, pridobljenih v preskušanju
- zagotavlja zaščito pravic in varnosti preiskovancev

Dobra klinična praksa

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

GUIDELINE FOR GOOD CLINICAL PRACTICE
E6(R1)

Current *Step 4* version
dated 10 June 1996

(including the Post Step 4 corrections)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Dobra klinična praksa

TABLE OF CONTENTS

Dobra klinična praksa

Dobra klinična praksa

Protokol kliničnega preskušanja

Dokument, ki predstavlja pisni dogovor med udeleženci kliničnega preskušanja in znanstveno skupnostjo.

Vsebuje:

- cilje, načrt in metodologijo kliničnega preskušanja zdravila
- način statistične obdelave podatkov
- organizacijo kliničnega preskušanja zdravila v skladu z dobro klinično prakso

Protokol - NASLOVNA STRAN

- naslov in številka protokola
- datum in verzija protokola
  - napisan pred začetkom kliničnega preskušanja oz. pred prijavo na Komisijo za medicinko etiko ter JAZMP
  - večje naknadne spremembe protokola je potrebno sporočiti Komisiji za medicinsko etiko ter JAZMP

Klinična raziskava

ODNOS MED FARMAKOKINETIKO IN FARMAKODINAMIKO FENTANILA PRI OTROCIH

Verzija 1

Datum: 08.07.2010

	Podpis:	Datum:
doc. dr. XX, dr. med.	_____	_____
doc. dr. XX, mag. farm.	_____	_____

Protokol – SODELUJOČI V RAZISKAVI

- ustanove
  - sponzor
  - preskuševalec
- posamezniki:
  - vodja projekta s strani sponzorja
  - glavni raziskovalec
  - monitor
  - avtor protokola
  - odgovorna oseba za analizo vzorcev
  - odgovorna oseba za statistiko
  - odgovorna oseba za klinično laboratorijsko diagnostiko

Protokol – IZHODIŠČA RAZISKAVE

- umestitev raziskave glede na rezultate predhodnih raziskav oz. glede na že znana dejstva o predmetu raziskave

Klinična raziskava

ODNOS MED FARMAKOKINETIKO IN FARMAKODINAMIKO FENTANILA PRI OTROCIH

Protokol – NAMEN RAZISKAVE

- osnovni oz. primarni namen
  - osnovno vprašanje na katerega bi radi dobili odgovor tekom preskušanja
  - na tem temelji določitev velikosti vzorca
- sekundarni nameni
  - navadno povezani s primarnim namenom
  - vrednotimo lahko enake ali druge parametre kot pri primarnem namenu

Protokol – NAMEN RAZISKAVE

Catheter Analgesia Trial (CATH)

This study has been completed.

First Received on October 9, 2008. Last Updated on September 13, 2011. History of Changes

Sponsor:	Loyola University
Information provided by (Responsible Party):	Loyola University
ClinicalTrials.gov Identifier:	NCT00771173

Purpose

The primary aim of this randomized clinical trial is to compare the utility of phenazopyridine HCl vs. placebo in reducing catheter-associated discomfort during the post-operative period in the gynecologic patient using mean VAS measurments.

The secondary aim is to compare overall post operative pain medication requirements, including cumulative dose and patterns of medication utilization between groups.

Condition	Intervention	Phase
Interstitial Cystitis	Drug: phenazopyridine HCl Other: Placebo	Phase IV

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: THE CAT(H) STUDY CATHETER ANALGESIA TRIAL Phenazopyridine vs. Placebo: a Randomized Controlled Trial A CREST 2010 Project

Protokol - PARAMETRI VREDNOTENJA

- definirani v skladu s primarnim in sekundarnimi nameni raziskave
- končni ali nadomestni izidi

Področje	Končni izid	Nadomestni izid
HIV pozitivni bolniki	▪ incidenca AIDS-a ▪ umrljivost	nivo CD-4 limfocitov
onkologija	umrljivosti	rast tumorja
kardiovaskularna obolenja	▪ umrljivost ▪ incidenca miokardnega infarkta	napredovanja ateroskleroze z UZ ali angiografijo

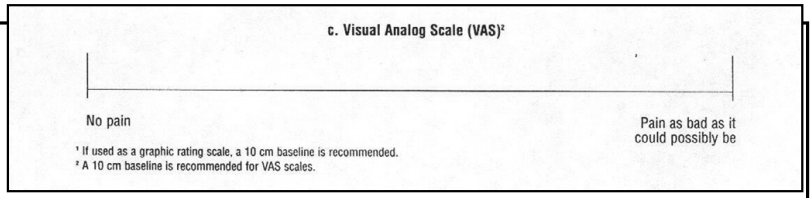
Protokol - PARAMETRI VREDNOTENJA

- nadomestni izidi
  - pogosto potrebno manjše število preizkušancev
  - lahko skrajšajo čas raziskave
  - potrebna zanesljiva korelacija mednadomestnim izidom in kliničnim dogodkom (nivo CD-4 limfocitov v krvi indikator za resnost AIDS-a)
  - nadomestni izid mora odražati celokupen učinek intervencije
    (neko zdravilo sicer ugodno vpliva na nivo holesterola v plazmi, poveča pa umrljivost)

Protokol - PARAMETRI VREDNOTENJA

- vrednotenje varnosti in učinkovitosti zdravljenja
  - klinične posledice bolezni oz. zdravljenja
    (smrt, incidenca obolenja, olajšanje simptomov, neželen učinek…)
  - fizične manifestacije bolezni
    (krvni tlak, velikost tumorja, FEV1)
  - laboratorijske vrednosti
    (glukoza, holesterol , hormoni v plazmi, konc. zdr. učinkovine v plazmi)
  - zadovoljstvo z uporabo preskušanega zdravila
  - strošek zdravljenja

Protokol - PARAMETRI VREDNOTENJA



Purpose

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Primary Purpose: Treatment

Official Title: THE CAT(H) STUDY CATHETER ANALGESIA TRIAL Phenazopyridine vs. Placebo: a Randomized Controlled Trial A CREST 2010 Project

Protokol - NAČRT RAZISKAVE

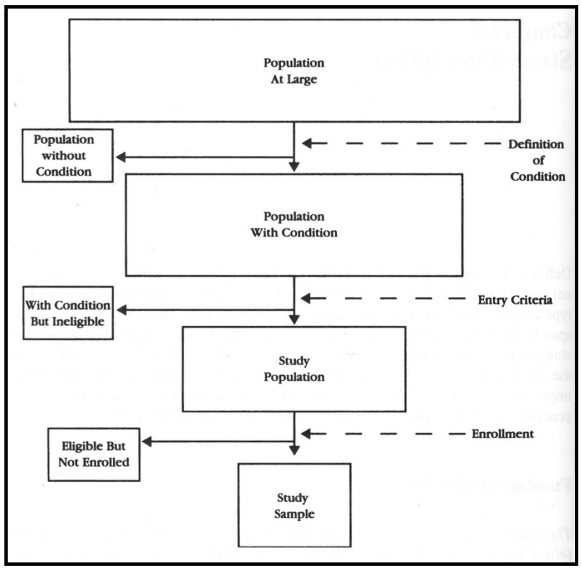
- vrsta raziskave (BEQ, FK, študija učinkovitosti, …)
- eden/več odmerkov zdravila
- eden/več preskuševalcev
- kontrolirana/nekontrolirana
- odprta/slepa raziskava
- shema randomizacije
- paralelna, navzkrižna, …

Protokol – ZDRAVILO V RAZISKAVI

- proizvajalec
- zdravilna učinkovina
- farmacevtska oblika
- jakost
- shranjevanje zdravila
  - mesto shranjevanja
  - čas shranjevanja
  - pogoji shranjevanja

Protokol – PREUČEVANA POPULACIJA

- del populacije, ki ustreza vnaprej definiranim kriterijem
- preizkušance izberemo iz preučevane populacije



Protokol – PREUČEVANA POPULACIJA

- vključitveni/izključitveni kriteriji
  - rasa
  - starost
  - spol
  - obolenja
  - terapije z zdravili
  - življenjske navade

  - **izločimo osebe, ki jim lahko intervencija škodi**
  - **izločimo osebe, ki jim intervencija prinaša premalo koristi**

Protokol – PREUČEVANA POPULACIJA

Vključitveni/izključitveni kriteriji

- Age 18 to 65 years.
- Men, and women who are post-menopausal, surgically sterile, or using acceptable birth control.
- Depression lasting at least six months, but no longer than one year.
- No previous depressive episodes.
- Not taking any other medications that might interfere with the study medication (list provided).
- Able to read and comprehend the informed consent document.
- Willing to sign the informed consent.
- Able to take pills.
- Able to make weekly visits to the clinic site for three months.

Protokol – PREUČEVANA POPULACIJA

Efficacy and Safety of Lornoxicam in Patients With Acute Coronary Syndrome (PLEA)

This study has been completed.

First Received on October 18, 2009. No Changes Posted

Sponsor:	Central Clinical Hospital of the Presidential Administration of the Russian Federation
Information provided by:	Central Clinical Hospital of the Presidential Administration of the Russian Federation
ClinicalTrials.gov Identifier:	NCT00997750

Purpose

The purpose of this study is to determine whether nonsteroidal antiinflammatory drug lornoxicam in combination with low dose aspirin (100mg/day) is effective and safe in patients with Acute Coronary Syndrome without persistent ST-segment elevation.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

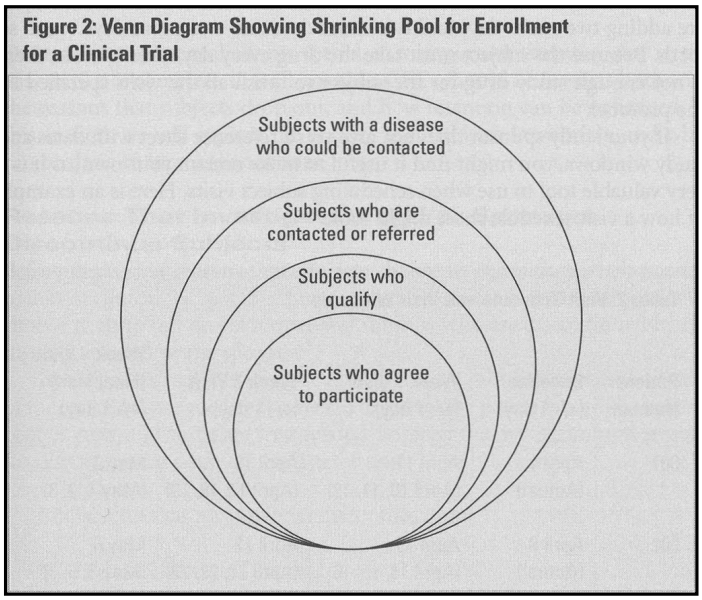
Inclusion Criteria:

1. Unstable angina verified during first 48 hours after admitting to the hospital or
2. Acute Miocardial infarction without St-segment elevation verified during first 48 hours after admitting to the hospital

Exclusion Criteria:

1. High risk of bleeding of any location
2. Any kind of acute and active inflammatory process (excluding acute coronary syndrome)
3. Aspirin or NSAID Intolerability
4. No informed consent
5. Acute peptic stomach or duodenum ulcer
6. Acute or chronic renal failure (serum creatinin >300 mmol/l)
7. Acute cerebrovascular bleeding

Protokol – PREUČEVANA POPULACIJA



Protokol – PREUČEVANA POPULACIJA

- postopek nabora preizkušancev
  (odvisen od preučevane populacije)
  - direktno povabilo s strani glavnega raziskovalca
  - registri bolnikov
  - uporaba medijev
  - masovna pošta
  - društva bolnikov

Protokol – PREUČEVANA POPULACIJA

Protokol – PREUČEVANA POPULACIJA

• "Chosen for their interdisciplinary nature and potential benefits to patients, these programs range from fundamental investigations of the origin of disease to advanced clinical trials in which patients have access to the latest and most promising treatments" (Press release, University of California, San Francisco, www.ucsf.edu/pressrel/2001/10/102501.html).

"Latest" and "most promising" are not the same as effective, however.

Protokol – PREUČEVANA POPULACIJA

• "Participants are among the first to receive new treatments before they are widely available" (Cancer Research Center of Hawaii, www.hawaii.edu/crch/SerCTBenefits.htm).

Unless, of course, participants receive a placebo or control drug.

Protokol – PREUČEVANA POPULACIJA

Research Study

Subjects needed for a study to investigate the effects of an investigational medicine on lessening the symptoms of the common cold.

Subjects must be seen by the second day of the cold and must be at least 18 years old.

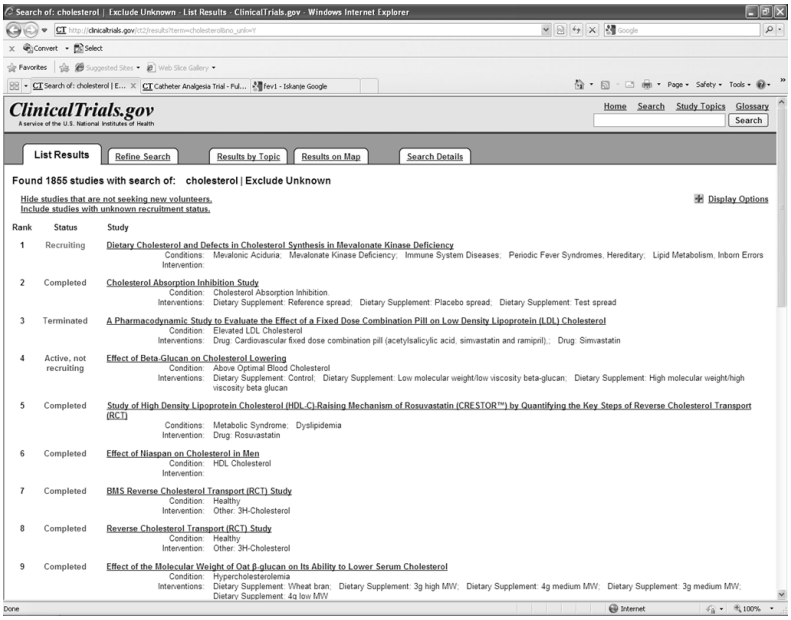
For details, contact Shirley Williams at Eastside Clinic. (222) 222-2000

Protokol – PREUČEVANA POPULACIJA

Informacije, ki jih je priporočljivo vključiti pri oglaševanju

1. Name and address of the investigator or research facility;
2. Condition under study and/or purpose of the research;
3. Brief summary of the primary criteria for study eligibility;
4. Brief list of benefits (e.g., no-cost health examination);
5. Time or other subject commitment; and
6. Contact information.[7]

Protokol – PREUČEVANA POPULACIJA



Protokol – IZBOR PREIZKUŠANCEV

- začetno vrednotenje posameznikov pri izboru preizkušancev
  - demografski podatki
  - zdravniški pregled
  - preiskave (EKG, UZ, …)
  - laboratorijske preiskave
  - genetski polimorfizmi

vključitveni/izključitveni kriteriji:
- rasa
- starost
- spol
- obolenja
- terapije z zdravili
- življenjske navade

Protokol – IZBOR PREIZKUŠANCEV

INSTITUTION CODE	PARTICIPANT ID	VISIT TYPE	VISIT DATE (MM/DD/YYYY)
_____	_____	_____	__ __/__ __/__ __ __ __

Answers to questions 1-10 must be **YES** for the subject to be eligible.
Criteria 4-8 may be evaluated using laboratory test results obtained during a time not to exceed four weeks prior to going on study.

	Criteria	Yes	No
1	The participant is male, and has localized, biopsy-proven adenocarcinoma of the prostate and planned radical prostatectomy	☐	☐
2	The participant is ≥ 18 years of age	☐	☐
3	ECOG performance status ≤ 2 (Karnofsky ≥ 60%)	☐	☐
4	Leukocytes are ≥ 3,000/µL	☐	☐
5	Platelets are ≥ 100,000/µL	☐	☐
6	Total bilirubin is within normal institutional limits	☐	☐
7	The AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional ULN	☐	☐
8	Creatinine is within normal institutional limits	☐	☐
9	The participant has agreed to use adequate contraception (barrier method of birth control or abstinence) prior to study entry and for the duration of study participation	☐	☐
10	Participant has the ability to understand and willingness to sign the informed consent	☐	☐

FORM 7-1 Inclusion criteria.

Protokol – IZBOR PREIZKUŠANCEV

- velikost vzorca
  (potrebno upoštevati potencialni izstop posameznikov iz raziskave)

A number of 24 healthy male volunteers will be included in this study.
The choice of the sample size n=20 to be used in the study is based on the published data. Lack of data regarding intrasubject variability of XXX makes the calculation of the sample size specifically for the present study impossible.
To guard against possible withdrawals due to the side effects of XXX 4 additional volunteers will be included in the study thus leading to a total sample of 24 volunteers.

Protokol – PREUČEVANA POPULACIJA

<u>Pediatrična populacija:</u>

- novorojenčki: 0 do 27 dni
- dojenčki: 1-23 mesecev
- otroci: 2-11
- mladostniki: 12-18 let

- razvojne, fiziološke in psihološke razlike glede na odrasle
- pri terapiji z zdravili razlike v:
  - farmakokinetiki
  - farmakodinamiki
  - neželenih učinkih

Protokol – PREUČEVANA POPULACIJA

Pediatrična populacija:

- vključena v klinična preskušanja:
  - če se preskušanje ne more enakovredno izvesti z odraslimi
  - je namen raziskave pridobiti informacije pomembne za zdravje otrok
- spodbujajo oz. vedno bolj se zahtevajo raziskave na pediatrični populaciji, če bodo zdravila po utrženju namenjena tej populaciji
- v raziskave ne vključujemo zdravih otrok (izjeme – npr. cepiva)

Protokol – PREUČEVANA POPULACIJA

Pediatrična populacija:

- vključuje se manj ranljive skupine (npr. starejši otroci)
- izbor preizkušancev mora biti čim bolj v skladu s tarčno populacijo testiranega zdravila
- čim manjša velikost vzorca (vendar zadosti za statistično analizo)
- uporaba placeba bolj omejena kot pri odraslih
- tekom preskušanja je potrebno čim bolj skrbeti za ugodje otroka
  - namestitev prilagojena otrokom
  - osebje z izkušnjami s pediatrično populacijo

Protokol – PREUČEVANA POPULACIJA

No or minimal risk	Minor increase over minimal risk	Greater than minor increase over minimal risk
– History taking – Clinical examination – Auxological measurements – Tanner staging – Behavioural testing – Psychological testing* – Quality of Life assessment – Venipuncture* – Heel prick* – Finger prick* – Subcutaneous injection – Urine collection with bag* – Breath condensate collection – Collection of saliva or sputum – Collection of hair sample – Collection of tissue removed from body as part of medical treatment* – Topical analgesia* – Stool tests – Bio-impedancemetry	– Urine collection via endo-luminal or suprapubic catheter – Arterial puncture – Umbilical catheter – pH metry – Nasogastric tube insertion and use – Transcutaneous oxygen or carbondioxide tension monitoring – Electrophysiological measurements (using stimulation) – Exercise testing (ergometry, spiroergometry) – Raised volume pulmonary function testing (infants) – Peripheral venous lines – Polysomnography – Fasting (≥ 1 meal) – Spinal CSF tap	– Heart catheterisation – Endoscopy – Biopsy – Surgery or modification of standard surgical procedure carried out as part of medical treatment – Sedation – Anaesthesia – Systemic analgesia – Hypoglycaemia test – Unstable isotope usage – PET scanning

Protokol – PREUČEVANA POPULACIJA

Pediatrična populacija:

- namesto krvnih vzorcev raje vzorčenje urina ali sline
- čim manjši volumen krvnih vzorcev

The following blood volume limits for sampling are recommended (although are not evidence-based). If an investigator decides to deviate from these, this should be justified. Per individual, the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1% at any single time. In the rare case of simultaneous trials, the recommendation of 3% remains the maximum. The total volume of blood is estimated at 80 to 90 ml/kg body weight; 3% is 2.4 ml blood per kg body weight.

Protokol – PREUČEVANA POPULACIJA

Ženske v rodni dobi:

- priporoča se vključitev žensk v klinična preskušanja
- nevarnost izpostavitve embrija ali ploda zdravilu v preskušanju
- potrebno izključiti nosečnost in obvezna uporaba kontracepcijskega sredstva

Kaj pa nosečnice?

Protokol – PREUČEVANA POPULACIJA

2.2. Why the Elderly Are Underrepresented in Clinical Trials

Elderly cancer patients are recruited for clinical trial participation less frequently than other populations. The research on this matter suggests a variety of reasons:

- Elderly patients often take an array of prescription and over-the-counter medications that can cause significant drug interactions when combined with treatment in clinical trials. Stopping or reducing dosage of these medications can be complicated if this is necessitated by trial requirements.
- The elderly may have considerably more difficulties in coping with trial logistics, especially costs and travel.

Protokol – PREUČEVANA POPULACIJA

2.2. Why the Elderly Are Underrepresented in Clinical Trials

- Some protocols may have unnecessarily strict exclusion requirements that by their nature rule out most of the elderly population. For example, very few elderly people have no preexisting conditions.
- Determining the appropriate dosage of new drugs being tested in the trial may present difficulties when working with older patients.
- There may be the general perception on the part of some health care professionals that elderly people are inherently too frail or even incompetent to participate in trials.

Protokol – NAČIN VREDNOTENJA PARAMETROV

Podrobno navedeni postopki in metode za:

- začetno vrednotenje posameznikov v fazi izbora preizkušancev
- aplikacijo zdravila v preskušanju
  - shema odmerjanja zdravila
  - vnos hrane, tekočine tekom preskušanja
  - druge omejitve tekom preskušanja

Protokol – NAČIN VREDNOTENJA PARAMETROV

Podrobno navedeni postopki in metode za:

- pridobivanje končnih in nadomestnih izidov v skladu s primarnim in sekundarnimi nameni raziskave
  - intervju, vprašalnik, ocenjevalna lestvica
  - fizični pregled
  - preiskave
  - laboratorijske meritve
- statistično obdelavo podatkov

Protokol – NAČIN VREDNOTENJA PARAMETROV

- ocenjevalna lestvica

Simptome odtegnitve bomo vrednotili s pomočjo modificirane Finneganove lestvice za vrednotenje neonatalnega abstinenčnega sindroma.

Simptome odtegnitve bomo vrednotili po prekinitvi infuzije fentanila in sicer jih bomo prvi dan ocenili 2, 4, 8 in 12 ur po prekinitvi infuzije, naslednje dni pa dvakrat dnevno.

VREDNOTENJE SIMPTOMOV ODTEGNITVE - FINNEGAN

Sistem	Znaki in simptomi	Točke	1. DAN				2. DAN		3. DAN	
			1. MERITEV	2. MERITEV	3. MERITEV	4. MERITEV	1. MERITEV	2. MERITEV	1. MERITEV	2. MERITEV
MOTNJE CENTRALNEGA ŽIVČNEGA SISTEMA	Piskav jok	2								
	Dolgotrajen piskav jok	3								
	Spi < 1 uro po hranjenju	3								
	Spi < 2 uri po hranjenju	2								
	Spi < 3 uri po hranjenju	1								
	Blag tremor, ko je vznemirjen	1								
	Zmeren-hujši tremor, ko je vznemirjen	2								
	Blag tremor, ko je miren	3								
	Zmeren-hujši tremor, ko je miren	4								
	Povečan mišični tonus	2								
	Odgnitne (navedi področje)	1								
	Mioklonični krči	3								
	Generalizirane konvulzije	5								
METABOLIČNE, VAZOMOTORIČNE, DIHALNE MOTNJE	Potenje	1								
	Vročina (37.5-38.3°C)	1								
	Vročina (38.4°C in več)	2								
	Pogosto zehanje (> 3-4 krat)	1								
	Zapolnjen nos	1								
	Kihanje (> 3-4 krat)	1								
	Širjenje nosnic	2								
	Hitrost dihanja > 60/min	1								
	Hitrost dihanja > 60/min z ugrezanjem	2								
GASTROINTESTINALNE MOTNJE	Prekomerno sesanje	1								
	Slabo hranjenje	2								
	Spahovanje, bruhanje	2								
	Bruhanje v kilu	3								
	Mehko blato	2								
	Vodeno blato	3								
	Celokupne točke									
	Začetnici ocenjevalca									

Protokol – NAČIN VREDNOTENJA PARAMETROV

- meritve koncentracije učinkovine v plazmi

Blood sampling schedule:

Twenty-two (22) blood samples (6-7 ml each) will be taken according to the following schedule: 0 (pre-drug administration)/ 0.25/ 0.5/ 0.75/ 1/ 1.5/ 2/ 3/ 4/ 6/ 8/ 12/ 16/ 24/ 36/ 48/ 60/ 72/ 96/ 120/ 144/ 168 hours post-drug.

Sampling and storage technique:

No more than 308 ml of blood will be taken over the two study phases.

Since DRUG exhibits saturable low-capacity binding to erythrocytes, hemolysis would affect results at low plasma concentration; therefore measures should be taken in order to prevent hemolysis of blood samples. If hemolysis happened, this must be described in the CRF.

Samples will be collected using direct venepuncture or an intravenous cannula in a forearm vein.

Protokol – NAČIN VREDNOTENJA PARAMETROV

- meritve koncentracije učinkovine v plazmi

Sampling and storage technique:

Blood samples will be collected into heparinized tubes and centrifuged within 10 minutes. Obtained plasma will be divided into polypropylene tubes with screw-caps. The tubes will be labeled with a code number that corresponds to subject, study period and sampling time, but does not reveal formulation identity.

The plasma samples will be capped and stored frozen at 18±4ºC until analysed.

The clock times of all blood sample draws will be recorded and reported for each subject.

Sample shipping

All samples will be delivered frozen to the analytical facility in XXX.

XY is responsible for the transport of blood samples. The transport will be documented.

Protokol – NAČIN VREDNOTENJA PARAMETROV

- pomembna je visoka kvaliteta zbranih podatkov
- glavne vrste napak
  - manjkajoči podatek
    - podatka dejansko ne uspemo pridobiti
    - podatek pozabimo pridobiti
    - podatek ne vnesemo v ustrezne formularje
  - nepravilen podatek
    - slabo umerjene aparature
    - napake pri vnosu podatkov v formularje
      (krvni tlak: izmerjen 84/124 mm Hg, vneseno 124/84 ali 84/142,)
    - ponarejeni podatki

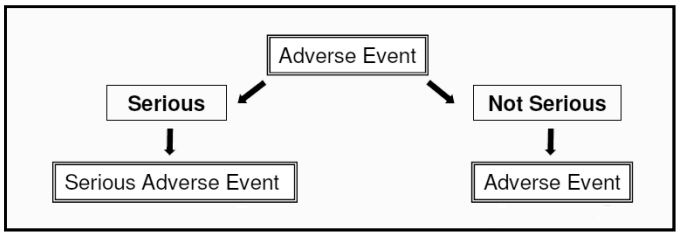
Protokol – NAČIN VREDNOTENJA PARAMETROV

- glavne vrste napak
  - velika variabilnost podatkov
    - zmanjša se verjetnost, da opazimo realne vplive
    - variabilnost je lahko posledica samega parametra, aparature ali raziskovalca
- pristopi za potencialno zmanjšanje napak pri zbiranju podatkov
  - jasno definirani postopki raziskav v protokolu
  - predhodno preverjanje postopkov
  - priročnik postopkov in standardni operativni postopki
  - testni listi
  - usposabljanje osebja, ki sodeluje pri pridobivanju podatkov
- pomemben je stalni nadzor nad kvaliteto podatkov

Neželeni dogodki tekom kliničnega preskušanja

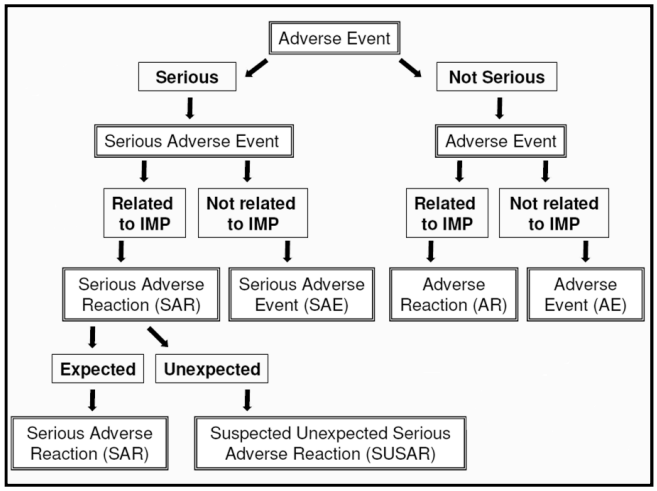
Resni neželeni dogodki

- ki se končajo s smrtjo
- ogrožajo življenje
- zahtevajo hospitalizacijo ali podaljšanje obstoječe hospitalizacije
- vodijo v dolgotrajno ali znatno nesposobnost oz. nezmožnost
- vodijo v okvare ploda



Neželeni dogodki tekom kliničnega preskušanja

Povezava neželenega dogodka z zdravilom v preskušanju
(verjetna, možna, malo verjetna, ni povezave, ni možno oceniti)



Neželeni dogodki tekom kliničnega preskušanja

- viri:
  - opazovanje
  - postopki v raziskavi
  - pogovor s preskušancem
  - spontano poročanje
- definiran mora biti čas, v katerem se beležijo neželeni učinki
- definirano kdo in kako skrbi za varnost preizkušancev med kliničnim preskušanjem

Protokol – VARNOST PREIZKUŠANCEV

Poročanje in dokumentiranje neželenih pojavov

- testni listi, posamična in periodična poročila o resnih neželenih škodljivih učinkih zdravil
- poročanje resnih neželenih škodljivih učinkov:
  - monitorju
  - osebi, ki je pri sponzorju odgovorna za farmakovigilanco
  - nacionalnemu centru za spremljanje neželenih škodljivih učinkov zdravil in medicinskih pripomočkov (Klinični center, Interna klinika, Center za zastrupitve, Ljubljana)
  - Javni agenciji za zdravila in medicinske pripomočke RS

Neželeni dogodki tekom kliničnega preskušanja

Omejitve pri identifikaciji neželenih učinkov zdravil tekom kliničnega preskušanja:

Table 1: Differences Between Clinical Trials and Marketed Use of a Product

Clinical Trials	Marketed Use
■ Relatively small number of patients	■ Millions of patients
■ Tight control	■ No control
■ Extra care	■ Standard care
■ Highly trained physicians	■ Any physicians
■ Narrow patient population	■ Anyone prescribed the drug

- navadno so preizkušanci manj rizični kot populacija, ki ji je zdravilo namenjeno
- v kliničnih preskušanjih niso zastopane vse podskupine populacije (nosečnice, doječe matere, starejši)
- relativno kratkotrajno preskušanje

Protokol – VARNOST PREIZKUŠANCEV

- kriteriji za izstop preizkušancev iz raziskave
  - odločitev preizkušanca
  - odločitev glavnega raziskovalca
    - pojav obolenja ali neželenega dogodka, ki predstavlja tveganje za zdravje posameznika ali pa lahko pomembno vpliva na rezultate raziskave
    - nespoštovanje protokola

Protokol – VARNOST PREIZKUŠANCEV

Our sponsor wants us to drop a subject from our study because he does not come in during the specified visit windows. He is a busy professional, and is often out of town during the visit times. Do we have to drop him?

Remember that compliance is ultimately a safety issue, as well as a statistical issue. You may discuss this with the sponsor, but the subject will probably need to be discontinued if he cannot adhere to the protocol requirements.

Protokol – VARNOST PREIZKUŠANCEV

Kaj lahko spodbudi preizkušanca, da izstopi iz raziskave?

- Having to wait when coming in for an appointment.
- Not being treated nicely and with respect.
- Not seeing the investigator or the coordinator, but being seen by a "substitute" that he or she doesn't know.
- Not seeing the same person at most visits (developing a one-to-one relationship).
- Being rushed and hurried through the appointment.
- Feeling that the investigator/coordinator doesn't really want to see him or her.
- Not being asked about how he or she feels and how the study is going for him or her.
- Not having the opportunity to ask questions.
- Being afraid to ask study-related questions.
- Being made to feel dumb or silly when asking questions.
- Being berated for doing something wrong.
- Having the investigator or coordinator disparage the study.

Klinično preskušanje - ETIČNI VIDIKI

- upoštevani morajo biti v vseh fazah kliničnega preskušanja
- raziskovalci in sponzor imajo etično zavezo do:
  - preizkušancev
  - znanosti
  - družbe

Klinično preskušanje - ETIČNI VIDIKI

TABLE 2-2 Ethical Framework for Clinical Research

Principles of Ethical Clinical Research	Description
Value	Research poses a clinically, scientifically, or socially valuable question that will contribute to generalizable knowledge about health or be useful to improving health. Research is responsive to health needs and priorities.
Validity	Study has an appropriate and feasible design and end points, rigorous methods, and feasible strategy to ensure valid and interpretable data.
Fair subject selection	The process and outcomes of subject and site selection are fair and based on scientific appropriateness, minimization of vulnerability and risk, and maximization of benefits.

Klinično preskušanje - ETIČNI VIDIKI

TABLE 2-2 Ethical Framework for Clinical Research

Principles of Ethical Clinical Research	Description
Favorable risk–benefit ratio	Study risks are justified by potential benefits and value of the knowledge. Risks are minimized and benefits are enhanced to the extent possible.
Independent review	Independent evaluation of adherence to ethical guidelines in the design, conduct, and analysis of research.
Informed consent	Clear processes for providing adequate information to and promoting the voluntary enrollment of subjects.
Respect for enrolled participants	Study attends to and shows respect for the rights and welfare of participants both during and at the conclusion of research.

Klinično preskušanje - ETIČNI VIDIKI

- randomizacija
- kontrolna skupina
- preskušanja v razvijajočih se državah
- varovanje podatkov
- verodostojnost podatkov
- navzkrižje interesov pri raziskovalcih

Klinično preskušanje - ETIČNI VIDIKI

S placebom kontrolirane raziskave:

- če v praksi ni učinkovite terapije
- če prekinitev učinkovite terapije pri posamzeniku povzroči kvečjemu prehodno neugodje ali zakasnitev olajšanja simptomov
- če uporaba v praksi učinkovite terapije kot kontrole ne bi dala znanstveno zanesljivih rezultatov in uporaba placeba ne bi povečala tveganja za resne in ireverzibilne negativne posledice pri posamezniku

Klinično preskušanje - ETIČNI VIDIKI

Navzkrižje interesov pri raziskovalcih:

- primarni interesi: zdravje in varnost preizkušancev, pridobivanje novih medicinskih znanj
- sekundarni interesi: finančna korist, napredovanje, prepoznavnost, objave rezultatov raziskave v pomembnih revijah, želja po slavi, ...
- navzkrižje interesov - sekundarni interesi prevladajo in čezmerno vplivajo na profesionalno presojo posameznika pri primarnih interesih
- lahko vzrok za subjektivnost v načrtu, izvedbi, analizi, interpretaciji in publikaciji kliničnega preskušanja

Protokol kliničnega preskušanja

Example 1. It is known that rheumatic fever can usually be prevented by adequate treatment of streptococcal respiratory infections by the parenteral administration of penicillin. Nevertheless, definitive treatment was withheld, and placebos were given to a group of 109 men in service, while benzathine penicillin G was given to others.

The therapy that each patient received was determined automatically by his military serial number arranged so that more men received penicillin than received placebo. In the small group of patients studied 2 cases of acute rheumatic fever and 1 of acute nephritis developed in the control patients, whereas these complications did not occur among those who received the benzathine penicillin G.

Protokol kliničnega preskušanja

Example 5. In this controlled, double-blind study of the hematologic toxicity of chloramphenicol it was recognized that chloramphenicol is "well known as a cause of aplastic anemia" and that there is a "prolonged morbidity and high mortality of aplastic anemia" and that "... chloramphenicol-induced aplastic anemia can be related to dose ...." The aim of the study was "further definition of the toxicology of the drug...."

Forty-one randomly chosen patients were given either 2 or 6 gm. of chloramphenicol per day; 12 control patients were used. "Toxic bone-marrow depression, predominantly affecting erythropoiesis, developed in 2 of 20 patients given 2.0 gm. and in 18 of 21 given 6 gm. of chloramphenicol daily." The smaller dose is recommended for routine use.

Protokol kliničnega preskušanja

Example 17. Live cancer cells were injected into 22 human subjects as part of a study of immunity to cancer. According to a recent review, the subjects (hospitalized patients) were "merely told they would be receiving 'some cells'"—"... the word cancer was entirely omitted. . . ." [Example 17 is the Jewish Chronic Disease Hospital Case, a discussion of which is included in this volume.—eds.]

Protokol kliničnega preskušanja

Example 19. During bronchoscopy a special needle was inserted through a bronchus into the left atrium of the heart. This was done in an unspecified number of subjects, both with cardiac disease and with normal hearts.

The technique was a new approach whose hazards were at the beginning quite unknown. The subjects with normal hearts were used, not for their possible benefit but for that of patients in general.

Protokol kliničnega preskušanja

Example 22. There is a question whether ureteral reflux can occur in the normal bladder. With this in mind, vesicourethrography was carried out on 26 normal babies less than forty-eight hours old. The infants were exposed to x-rays while the bladder was filling and during voiding. Multiple spot films were made to record the presence or absence of ureteral reflux. None was found in this group, and fortunately no infection followed the catheterization. What the results of the extensive x-ray exposure may be, no one can yet say. [. . .]

Protokol - ETIČNI VIDIKI

- podpisane izjave raziskovalcev, da bodo klinično preskušanje izvedli v skladu s protokolom raziskave ter v preskušanju spoštovali sodobna etična načela ter veljavno zakonodajo s tega področja
- pogoji za začetek kliničnega preskušanja
- zavarovanje odgovornosti
  - odgovornost sponzorja
  - plačilo odškodnine preizkušancu in nadomestilo za ustrezno nego v primeru škode, ki nastane kot posledica kliničnega preskušanja zdravila;

Protokol - ETIČNI VIDIKI

- zaupnost podatkov:
  - osebni podatki preizkušanca na vpogled samo za klinično preskušanje zdravila pooblaščenim osebam
  - preizkušanec obveščen o vsaki zanj pomembni informaciji v zvezi s kliničnim preskušanjem zdravila
  - tajne oznake (kode) preizkušanca in zdravila v kliničnem preskušanju, ki se lahko razkrijejo le v nujnih primerih
  - raziskovalci lahko objavijo rezultate preskušanja le z odobritvijo sponzorja

Protokol - ETIČNI VIDIKI

Povračilo stroškov:

- plačilo predvsem zdravim preizkušancem
- preizkušanec je upravičen do povračila neposrednih stroškov, ki nastanejo v zvezi z njegovo udeležbo v kliničnem preskušanju zdravila
- jasno mora biti določeno, kdaj preizkušanec dobi nadomestilo in kdaj ne
- več modelov plačila
  - plačilo na osnovi ponudbe in povpraševanja
  - plačilo po urni postavki z dodatki za neprijetne postopke
  - izključno plačilo stroškov, ki jih ima preizkušanec

Protokol - PROSTOVOLJNI PRISTANEK

Informiranje preizkušancev o kliničnem preskušanju:

- ustna in pisna razlaga
- prostovoljni pristanek:

  pisna oblika prostovoljnega pristanka preizkušanca, ali v primeru otroka ali za odločanje nezmožne osebe njenega zakonitega zastopnika, da sodeluje v kliničnem preskušanju zdravila, ki je podan potem, ko je preizkušanec oz. njegov zakoniti zastopnik podrobno pisno obveščen o vseh, za njega pomembnih podatkih o kliničnem preskušanju zdravila;

Protokol - PROSTOVOLJNI PRISTANEK

Prostovoljni pristanek – obvezne vsebine

- A statement that *the study involves research*, the *purpose* of the research, *duration* of the subject's participation, a *description of procedures* to be followed, and identification of any *procedures that are experimental*.
- A description of any reasonably foreseeable *risks or discomfort* to the subjects.
- A description of any *benefits* to the subjects or others that can reasonably be expected from the research.
- A disclosure of appropriate *alternate procedures* or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which *confidentiality of records* identifying the subject will be maintained and that notes the possibility that the FDA may inspect the records.

Protokol - PROSTOVOLJNI PRISTANEK

Prostovoljni pristanek – obvezne vsebine

- For research involving more than minimal risk, an explanation as to whether any *compensation* and an explanation as to whether any *medical treatments* are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of *whom to contact* for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is *voluntary*, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Protokol - PROSTOVOLJNI PRISTANEK

Prostovoljni pristanek – dodatne vsebine

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable.
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
- Any additional costs to the subject that may result from participation in the research.
- The consequences of the subject's decision to withdraw from the research and procedures for orderly termination of participation of the subject.
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the study subject.
- The approximate number of subjects involved in the study.

Protokol - PROSTOVOLJNI PRISTANEK

The Process of Informed Consent

Elements of Informed Consent	Description
Disclosure of information	Information about the study is disclosed that is based on a "reasonable" person standard. Disclosure takes into account subjects' language, education, familiarity with research, and cultural values. Both written information and discussion are usually provided.
Understanding	Understanding of the purpose, risks, benefits, alternatives, and requirements of the research.
Voluntary decision making	Free from coercion and undue influence. Free to choose not to enroll.
Authorization	Usually given by a signature on a written consent document.

Protokol - PROSTOVOLJNI PRISTANEK

The Process of Informed Consent

Elements of Informed Consent	Considerations and Challenges
Disclosure of information	There is a need to balance the goal of being comprehensive with that of attention to the amount and complexity of information in order to give participants the information they need and facilitate understanding.
Understanding	Empirical data show that participants often do not have a good understanding of the details of the research.
Voluntary decision making	Many possible influences affect participants' decisions about research participation. Avoid controlling influences.
Authorization	For some individuals or communities, requiring a signature reflects lack of appreciation for their culture or literacy level.

Protokol - PROSTOVOLJNI PRISTANEK

Pediatrična populacija

"In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if: (a) the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor;

(b) the minor has received information according to its capacity of understanding, from staff of experience with minors, regarding the trial, the risks and the benefits;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principle investigator;"

Protokol - PROSTOVOLJNI PRISTANEK

Pediatrična populacija:

- privolitev otroka
  - **NAMEN:** informiranje otroka in možnost soodločanja
  - prilagojeno zmožnosti otroka
  - upošteva se starost otroka, njegov razvoj, intelektualne zmožnosti, že predhodne izkušnje z boleznijo, ...
    - otroci 0-3 leta
    - otroci 3-11 let
    - mladostniki

Protokol - PROSTOVOLJNI PRISTANEK

List of items recommended to be covered in the information sheets:

1. What is the purpose of the trial?
2. Why have I been chosen?
3. Do I have to take part?
4. What will happen to me if I take part?
5. What are the compensations?
6. What will I have to do?
7. What is the medicine that is being tested?
8. What are the alternatives for diagnosis or treatment?
9. What are the possible disadvantages and risks of taking part?
10. What are the side effects of any treatment received when taking part?
11. Is ionising radiation to be received, and which regulations are respected?
12. Is there possible harm to an unborn child?
13. What are the possible benefits of taking part?
14. What happens when the research study stops?
15. What if there is a problem?
16. Will my taking part in the trial be kept confidential?
17. What will happen if I don't want to carry on with the trial?
18. What are the options if I stop taking part in the trial?
19. How is my General Practitioner/Family doctor involved?
20. What will happen to any samples taken from my body?
21. Will any genetic tests be done?
22. What will happen to the results of the research trial?
23. Who is organising and funding the research?
24. Who has reviewed the trial and what are the results?
25. Contact details for information or complaints

Protokol - DOKUMENTACIJA

Določeno mora biti:

- kje in pod kakšnimi pogoji se shranjujejo podatki pridobljeni tekom kliničnega preskušanja
- koliko časa se shranjujejo
- komu so dostopni

Protokol - DOKUMENTACIJA

TABLE 7-1 Source Documents

Original lab reports
Pathology reports
Surgical reports
Physician progress notes
Nurses notes
Medical record
Letters from referring physicians
Original radiological films
Tumor measurements
Patient diary
Patient notes
Patient interview
Hospital records/discharge summary/emergency room visit

Protokol - DOKUMENTACIJA

Dobra klinična praksa:

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.2.1	INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	INFORMATION GIVEN TO TRIAL SUBJECT		X	X
	- INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent		
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X