Univerza v Ljubljani
Fakulteta *za farmacijo*

Prijava raziskave na Komisijo za klinična preskušanja, JAZMP in Komisijo za medicinsko etiko

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Univerza v Ljubljani, Fakulteta za farmacijo
Katedra za biofarmacijo in farmakokinetiko

December, 2010

Vsebina predavanja

- Osnovna dokumenta
  - Pravilnik o kliničnem preskušanju
  - Zakon o zdravilih
- Komisije
  - Komisija za medicinsko etiko
  - Komisija za klinična preskušanja
- Prijava kliničnega preskušanja
  - Vloga za Komisijo za medicinsko etiko
    - Izjava o zavestni in svobodnia privolitvi sodelujočih
  - Vloga za Komisijo za klinična preskušanja
    - Enoten evropski obrazec za odobritev oz. priglasitev kliničnega preskušanja

Klinično preskušanje zdravil v RS

- Opredeljeno z dvema glavnima dokumentoma:
  - **ZAKON O ZDRAVILIH** (Uradni list RS, št. 31, 23.4. 2006)
    - III. Preskušanje zdravil (54. – 65. člena)
    - analizno, neklinično farmakološko-toksikološko in klinično preskušanje
    - klinično preskušanje – vrsta in namen, predpogoji/pogoji, zavarovanje odgovornosti, nadzor, **odobritev/priglasitev**, spremembe, prekinitev, plačilo stroškov
  - **PRAVILNIK o kliničnem preskušanju zdravil** (Uradni list RS, št. 54, 25.5. 2006)
    - Splošne odločbe, udeleženci, **odobritev/priglasitev**, spremembe, obveščanje o resnih neželenih učinkih, označevanje, shranjevanje dokumentacije, nadzor

Klinično preskušanje zdravil v RS

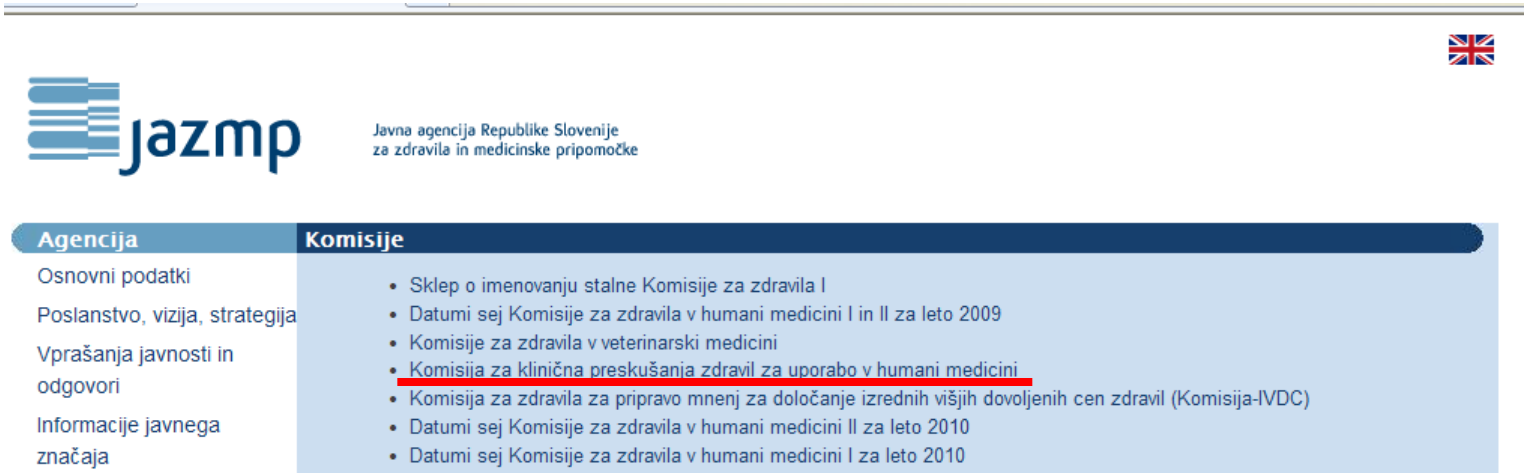
Vloga za odobritev/priglasitev kliničnega preskušanja (KP)

- Komisija za klinična preskušanja (KKP) zdravil
  - JAZMP
  - Mnenje o predlaganem oz. priglašenem KP
  - Vlogo opredeljuje Pravilnik o KP

- Nacionalna komisija za medicinsko etiko (KME)
  - Ministrstvo za zdravje
  - Etična sprejemljivost kliničnega preskušanja
  - Vloga napisana v skladu z navodili za pripravo vloge KME za presojo etičnosti raziskovalnega predloga

Komisija za klinična preskušanja zdravil

- Javna agencija RS za zdravila in medicinske pripomočke (JAZMP)



- Vloga
  - Mnenje o predlaganem oz. priglašenem KP - skladnost s pravilnikom o KP

Komisija za klinična preskušanja zdravil

- Sestava

KOMISIJA ZA KLINIČNA PRESKUŠANJA ZDRAVIL ZA UPORABO V HUMANI MEDICINI

Ministrica za zdravje, Zofija Mazej Kukovič je v Komisijo za klinična preskušanja zdravil za uporabo v humani medicini (Sklep št. 012-27/2008-1 z dne 7.5.2008 in št. 012-27/2008-3 z dne 2.7.2008) imenovala naslednje člane:

- Prof. dr. Tadej Battelino dr.med.,
- Dr. Mitja Kos mag.farm.,
- Prof.dr. Peter Rakovec dr.med.,
- Prof.dr. Matjaž Zwitter dr.med.

Komisija se sestaja praviloma vsakih šest tednov, datumi v naprej niso določeni.

dr. Martina Cvelbar, mag.farm., spec. l.r.
direktorica

Nacionalna komisija za medicinsko etiko

- Vse informacije na http://www.kme-nmec.si/

Nacionalna komisija za medicinsko etiko

- Samostojno in neodvisno ocenjuje etično sprejemljivost biomedicinskih raziskav na človeku
  (skrb za varstvo pravic, varnosti in dobrobiti preizkušancev).

- Poda mnenje o :
  - protokolu študije
  - ustreznosti raziskovalcev
  - zadostnosti prostorov
  - metodah in dokumentih, ki naj bi se uporabili za obveščanje preizkušancev in pridobitev njihovega prostovoljnega pristanka

Nacionalna komisija za medicinsko etiko

Pravilnik o sestavi, nalogah, pristojnostih in načinu dela komisije za medicinsko etiko (Uradni list št. 30, 2. 6. 1995)

- predsednik + 12 članov
- imenuje minister za zdravje

Člani Državne komisije za medicinsko etiko

(imenovani septembra 2009)

Prof. dr. **Jože Balažic**, dr. med.
zdravnik specialist sodne medicine, deontolog
Inštitut za sodno medicino
Medicinska fakulteta, Univerza v Ljubljani

Prof. dr. **Eldar Gadžijev**, dr. med.
zdravnik specialist abdominalni kirurg
Onkološki inštitut Ljubljana

Doc. dr. **Roman Globokar**, univ. dipl. teol.
teolog, profesor vere in kulture, asistent za moralno teologijo

Prof. dr. **Matija Horvat**, dr. med.
upok. zdravnik specialist kardiolog, intenzivist
Univerzitetni klinični center

Prof. dr. **Marga Kocmur**, dr. med.
zdravnik specialist psihiater, zasebnik
PKM d.o.o.

Prof. dr. **Damjan Korošec**, univ. dipl. prav.
Katedra za kazensko pravo
Pravna fakulteta, Univerza v Ljubljani

Prof. dr. **David Neubauer**, dr. med.
zdravnik specialist pediater
Klinični oddelek za otroško, mladostniško in razvojno nevrologijo
Pediatrična klinika, Univerzitetni klinični center

Doc. dr. **Tone Pačnik**, univ. dipl. psih.
klinični psiholog
Center za mentalno zdravje
Psihiatrična klinika

Prim. dr. **Dušica Pleterski-Rigler**, dr. med.
upok. zdravnica specialistka pediatrije infektologinja
Klinika za infekcijske bolezni in vročinska stanja, Univerzitetni klinični center

Prof. dr. **Pavel Poredoš**, dr. med.
zdravnik specialist internist angiolog
Klinični oddelek za žilne bolezni
Interna klinika, Univerzitetni klinični center

Doc. dr. **Janez Primožič**, dr. med.
zdravnik specialist pediater
Klinični oddelek za otroško kirurgijo in intenzivno terapijo
Kirurška klinika, Univerzitetni klinični center

Prof. dr. **Jože Trontelj**, dr. med.
zdravnik specialist nevrolog
Inštitut za klinično nevrofiziologijo
Nevrološka klinika, Univerzitetni klinični center

Dr. **Božidar Voljč**, dr. med.
upok. zdravnik specialist družinske medicine
Zavod RS za transfuzijsko medicino

Doc. dr. **Marjetka Zorman-Terčelj**, dr. med.
zdravnica specialistka interne medicine
Klinični oddelek za pulmologijo
Interna klinika, Univerzitetni klinični center

Tone Žakelj
strokovni sodelavec
Inštitut za klinično nevrofiziologijo
Nevrološka klinika, Univerzitetni klinični center

Nacionalna komisija za medicinsko etiko

- **Naloga komisije** je proučevanje in obravnava vprašanj s področja medicinske etike in deontologije ter dajanje mnenj in pojasnil o posamičnih vprašanjih s tega področja

- Komisija v skladu z zakonom **daje soglasja**:

– k predlogom znanstvenoraziskovalnih projektov s področja zdravstva,

– za preizkušanje še nepreverjenih metod preprečevanja in odkrivanja bolezni in poškodb, zdravljenja in rehabilitacije,

– **za preizkušanje zdravil**,

– za opravljanje drugih biomedicinskih raziskav

- Komisija na predlog ministra **proučuje tudi pobude** za še ne priznane oblike in metode diagnostike, zdravljenja in rehabilitacije, še zlasti tiste, ki niso v skladu s sprejetimi načeli medicinske znanosti, z vidika možne škodljivosti za zdravje ljudi in daje ministru mnenje o njihovi uporabi.

Pravilnik o sestavi, nalogah, pristojnostih in načinu dela komisije za medicinsko etiko (Uradni list št. 30, 2. 6. 1995)

Nacionalna komisija za medicinsko etiko

- Komisija lahko **od predlagateljev zahteva**, da vlogi priložijo tudi ustrezne ekspertize priznanih strokovnjakov, ki jih izbere komisija.

- Komisija lahko **daje mnenje** in opredelitve do posameznih medicinsko etičnih vprašanj ministru, Zdravstvenemu svetu, zbornicam ali drugim organom tudi **na lastno pobudo**. Komisija lahko glede določenih vlog za mnenja o etični neoporečnosti raziskav iz svoje pristojnosti zaprosi za mnenje področne komisije za medicinsko etiko, ki jih lahko ustanovijo posamezni večji zdravstveni zavodi. Področne komisije o svojem delu in odločitvah poročajo komisiji. Komisija sodeluje s pravno-etično komisijo pri Zdravniški zbornici Slovenije in z drugimi sorodnimi organi.

- **Zoper odločitve komisije ni pritožbe**. Če o posameznem medicinsko etičnem vprašanju Odbor za bioetiko Sveta Evrope ali pristojni organ Svetovne zdravstvene organizacije odloči ali zavzame drugačno stališče, je komisija dolžna to vprašanje ponovno obravnavati.

Pravilnik o sestavi, nalogah, pristojnostih in načinu dela komisije za medicinsko etiko (Uradni list št. 30, 2. 6. 1995)

Nacionalna komisija za medicinsko etiko

- Ocenjevanje etičnih vidikov raziskav
  - Konvencija o človekovih pravicah v zvezi z biomedicino, Oviedska konvencija
  - Priporočilo Sveta Evrope, Etično ocenjevanje biomedicinskih raziskav v Evropi (CDBI-CO-GT2)
  - Navodila o dobri klinični praksi KME

Poslovnik Komisije Republike Slovenije za medicinsko etiko, 28.8. 1998

Prijava kliničnega preskušanja na KME in KKP

- odločitev za klinično raziskavo
- prijava študije
  - Komisija RS za medicinsko etiko (KME)
  - Javna agencija RS za zdravila in medicinske pripomočke (JAZMP)

    (Komisija za klinična preskušanja - KKP)
- organizacija in izvedba kliničnega preskušanja
- analiza FK in FD podatkov
- statistična obdelava podatkov
- končno poročilo

Prijava kliničnega preskušanja na KME

- Klinične študije so znanstveno utemeljene in v vseh pogledih vodene z etičnimi načeli.
- Klinične študije se izvajajo v skladu s Helsinško deklaracijo o etičnih načelih za zdravstvene raziskave, ki vključujejo ljudi (WHO 1996).
- Pravice, varnost in dobro počutje preizkušancev imajo prednost pred interesi znanosti in družbe.

Priprava vloge KME za presojo etičnosti raziskovalnega predloga

Vsebina vloge:

1. Poln naslov in morebitno šifro raziskave.

2. Ime vodje raziskave oz. odgovornega raziskovalca, podatke o strokovni usposobljenosti in njegov kratek življenjepis (če še nima šifre raziskovalca pri Agenciji za raziskovalno dejavnost). Ime ustanove, ki predlaga raziskavo, in ustanove, na kateri bo raziskava potekala.

3. Ime in usposobljenost zdravnika, odgovornega za varnost oseb v raziskavi.

4. Načrt in protokol raziskave, vključno:
   - namen in znanstvena utemeljitev, podprta s pregledom bistvene literature
   - metode (tudi statistične)
   - recenzija znanstvene veljavnosti raziskave (če je na razpolago)
   - predlagateljeva ocena etičnih vidikov raziskave (možne koristi / tveganja in obremenitve)
   - povzetek v jeziku, ki je razumljiv ljudem brez medicinske izobrazbe.

Priprava vloge KME za presojo etičnosti raziskovalnega predloga

Vsebina vloge:

5. Osebe, ki bodo povabljene v raziskavo:
   - način pridobivanja prostovoljcev (ali drugih udeležencev)
   - izjava predlagatelja, da vabila ne bo spremljal pritisk ali neprimerno napeljevanje
   - merila za vključitev, nevključitev, izključitev, predvideno število
   - informacija o denarnem ali kakšnem drugačnem nadomestilu udeleženim osebam.

6. Kako bo poskrbljeno za varnost in koristi oseb v raziskavi
   - narava in verjetnost predvidljivega tveganja za zdravje udeleženih oseb
   - opis ukrepov za preprečevanje oz. ublažitev posledic neugodnih dogodkov
   - če gre za možnost mutagenih ali teratogenih učinkov, kakšni ukrepi so predvideni.

7. Če je predvidena primerjalna skupina bolnikov, kako bodo zavarovane njihove koristi.

Priprava vloge KME za presojo etičnosti raziskovalnega predloga

- **Vsebina vloge:**

8. Kako bo varovana zaupnost osebnih podatkov prostovoljcev v raziskavi.

9. Ali bodo udeležencem dostopni podatki o njihovem zdravju in rezultati raziskave.

10. Kdo je naročnik in plačnik raziskave (ime, naslov, odgovorni koordinator; isto tudi za morebitnega organizatorja raziskave (CRO)). Nadalje:
    kako so zavarovane za morebitno škodo na zdravju (kopija zavarovalne police)
    informacija o morebitnih plačilih ali nagradah raziskovalcem in njihovim sodelavcem v raziskavi.

11. Ali je predlog te raziskave (ali širše raziskave, katere del je predlagana raziskava) že ocenjevala kakšna komisija za etiko. Predložiti podatke in oceno.

Priprava vloge KME za presojo etičnosti raziskovalnega predloga

- **Vsebina vloge:**

12. **Izjava predstojnika ustanove ali oddelka**, na katerem bo tekla raziskava, ali strokovnega predstojnika ali mentorja odgovornega raziskovalca, **da so vključeni raziskovalci usposobljeni za delo** v zvezi z raziskavo, da so **zmožni pravočasno prepoznati** morebitne zaplete, ki bi lahko ogrožali zdravje ali življenje oseb v raziskavi, in da so **zmožni pravilno ukrepati**; da je na ustanovi poskrbljeno za strokovnost dela in varnost oseb v raziskavi; da bo nadziral raziskovalce, da se bodo **držali načel Helsinške deklaracije** o biomedicinskih raziskavah na človeku, **določil Konvencije Sveta Evrope** o varovanju človekovih pravic in dostojanstva človeškega bitja v zvezi z uporabo biologije in medicine (Oviedske konvencije) in **načel slovenskega Kodeksa medicinske deontologije**.

13. **Izjava odgovornega raziskovalca**, da se bo **držal načel Helsinške deklaracije** o biomedicinskih raziskavah na človeku, **določil Konvencije Sveta Evrope** o varovanju človekovih pravic in dostojanstva človeškega bitja v zvezi z uporabo biologije in medicine (Oviedske konvencije) in **načel slovenskega Kodeksa medicinske deontologije**. Izjava odgovornega raziskovalca in njegovega predstojnika o morebitnem konfliktu interesov (npr. o možnem finančnem interesu za določen izid raziskave).

Priprava vloge KME za presojo etičnosti raziskovalnega predloga

- **Vsebina vloge:**

12. Izjava predstojnika ustanove ali oddelka

Izjava strokovnega direktorja...(klinična ustanova)

Kot strokovni direktor ...., izjavljam, da so raziskovalci vključeni v raziskavo »NASLOV RAZISKAVE + ŠIFRA RAZISKAVE«, usposobljeni za izvajanje raziskave in so zmožni prepoznati možne zaplete na zdravju vključenih oseb ter so v tem primeru zmožni tudi pravilno ukrepati. V klinični ustanovi poskrbljeno za strokovnost dela in varnost oseb v raziskavi. Raziskovalce bom nadzirala pri upoštevanju načel Helsinške deklaracije o biomedicinskih raziskavah na človeku, določil Oviedske konvencije in načel slovenskega Kodeksa medicinske deontologije. Spoštovana bodo tudi načela Havajske deklaracije.

Ime in priimek strokovnega direktorja:
Klinična ustanova:
Podpis:

Izjava predstojnika Oddelka ... (Klinične ustanove)

Kot predstojnik Oddelka ..., izjavljam, da so raziskovalci vključeni v raziskavo »NASLOV RAZISKAVE + ŠIFRA RAZISKAVE«, usposobljeni za izvajanje raziskave in so zmožni prepoznati možne zaplete na zdravju vključenih oseb ter so v tem primeru zmožni tudi pravilno ukrepati. Na Oddelku ... je poskrbljeno za strokovnost dela in varnost oseb v raziskavi. Raziskovalce bom nadziral pri upoštevanju načel Helsinške deklaracije o biomedicinskih raziskavah na človeku, določil Oviedske konvencije in načel slovenskega Kodeksa medicinske deontologije. Spoštovana bodo tudi načela Havajske deklaracije.

Ime in priimek predstojnika Oddelka:
Klinična ustanova:
Podpis:

Priprava vloge KME za presojo etičnosti raziskovalnega predloga

- **Vsebina vloge:**

13. Izjava odgovornega raziskovalca

Izjava odgovornega raziskovalca za klinično preskušanje

Podpisan ... (odgovorni raziskovalec)., izjavljam, da se bom pri celotnem izvajanju raziskave držal načel Helsinške deklaracije o biomedicinskih raziskavah na človeku, Konvencije Sveta Evrope o varovanju človekovih pravic in dostojanstva človeškega bitja v zvezi z uporabo biologije in medicine (Oviedske konvencije) in načel slovenskega Kodeksa medicinske deontologije. Spoštoval bom tudi načela Havajske deklaracije.

Ime in priimek odgovornega raziskovalca:
Klinična ustanova:
Podpis:

Izjave ostalih odgovornih raziskovalcev - klinični, bioanalitski, statistični...

Priprava vloge KME za presojo etičnosti raziskovalnega predloga

- **Vsebina vloge:**

14. **<u>Obrazec izjave o zavestni in svobodni privolitvi sodelujočih</u>** zdravih oseb ali bolnikov v raziskavi, ki jo bodo podpisovali preiskovanci (oz. izjave o soglasju, ki jo bodo podpisovali zakoniti zastopniki, če gre za osebe, ki niso sposobne samostojne privolitve) po primerni in razumljivi ustni in pisni poučitvi o morebitnih koristih, neprijetnostih in tveganjih. Obvestilo oz. pojasnila za sodelujoče prostovoljce. Navedba naslova in telefonske številke zdravnika, pri katerem lahko oseba v raziskavi dobi nujno medicinsko pomoč v primeru resnega neugodnega pojava.

15. Informacija, kako naj osebe v raziskavi v nujni situaciji vzpostavijo stik z odgovornim zdravnikom

16. V raziskavah, kjer obstaja nevarnost teratogenosti in v katerih sodelujejo prostovoljke v rodni dobi (zdrave ali bolne): pisno pojasnilo o nevarnosti in izjava o tem, da se bodo udeleženke zavarovale pred zanositvijo, vse dokler ne mine nevarnost teratogenih učinkov na plod.

17. Datum oddaje vloge in podpis predlagatelja

Priprava vloge KME za presojo etičnosti raziskovalnega predloga

- **Obveščanje KME po odobritvi:**

18. Po odobritvi raziskave morate na KME nasloviti tudi:

    - morebitne spremembe protokola, ki kakorkoli spreminjajo etične vidike že odobrene raziskave
    - poročila o resnih neugodnih dogodkih, ki prizadevajo zdravje udeležencev (gl. tudi naslednjo točko)
    - obvestilo o morebitni predčasni prekinitvi raziskave in razlogih zanjo
    - obvestilo o končanju raziskave in sumarično končno poročilo, četudi so rezultati raziskave negativni.

19. Poročila o resnih nepredvidenih reakcijah (suspected unexpected serious adverse reactions, SUSAR) in o resnih neugodnih dogodkih (severe adverse events, SAE)

    - Brez odlašanja poročajte o resnih nepričakovanih zapletih, ki spreminjajo varnostno oceno in s tem tudi razmerje med tveganjem in koristjo, kot je bilo ocenjeno pred začetkom študije oz. je bilo ocenjeno kot sprejemljivo. Tu je všteta tudi nepričakovana pogostnost sicer pričakovanih zapletov. To pravilo se nanaša na vsa pomembna registrirana opažanja, povezana z raziskovanim zdravilom ali substanco, torej tudi v drugih študijah ali zunaj njih.

    - Iz multicentričnih kliničnih preskušanj, ki se izvajajo tudi v Sloveniji, pričakujemo poročila o resnih nepričakovanih zapletih (SUSAR), ki so se zgodili pri nas.

Priprava vloge KME za presojo etičnosti raziskovalnega predloga

- **Obveščanje KME po odobritvi:**

19. Poročila o resnih nepredvidenih reakcijah (suspected unexpected serious adverse reactions, SUSAR) in o resnih neugodnih dogodkih (severe adverse events, SAE)

    - Neželeni učinek / dogodek
      (vzrok povezan z zdravilom/vzrok ni povezan z zdravilom)
    - Resni neželeni dogodki (smrt, ogrožajo življenje, zahtevajo hospitalizacijo, invalidnost...)
    - Nepredvidljiv dogodek (ni zajet v brošura za raziskovalca, dosje o zdravilu v preskušanju ali SMPC)

Priprava vloge KME za presojo etičnosti raziskovalnega predloga

- **Seje in odgovor KME na vlogo:**

22. Komisija se sestaja enkrat mesečno. Vloga je zanesljivo obravnavana na prvi tekoči seji, če gradivo prispe vsaj en teden prej (in ni potrebna še recenzija zunaj KME). V nujnem primeru lahko zaprosite predsednika KME za vnaprejšnjo odobritev, ki jo nato lahko dokončno potrdi Komisija na prvem rednem sestanku. Vlogo pošljite v enem izvodu na naslov:

    - Prof. dr. Jože Trontelj, dr. med., predsednik KME
    - Inštitut za klinično nevrofiziologijo, Klinični center, 1525 Ljubljana.
    - Po elektronski pošti KME vlog še ne more sprejemati.

23. KME je dolžna na vlogo pisno odgovoriti v 60 dneh od prejema vloge, navadno pa ga pošlje v dveh do treh tednih po seji, na kateri je vlogo obravnavala, in sicer na naslov iz zaglavja vašega osnovnega dopisa. Če želite, da kopijo odgovora pošljemo še komu (naročniku raziskave, mentorju idr.), nam to sporočite v dopisu k vlogi, kjer - seveda - navedite tudi njegov naslov. Navedite tudi morebitne druge želje, npr. da potrebujete dva originalno podpisana odgovora, seznam članov KME, ki so bili na seji, ko je bila vloga obravnavana, potrjen seznam dokumentov, ki sestavljajo vašo vlogo ipd.

Zavestna in svobodna privolitev sodelujočih

- Definicije

  - pisna oblika odločitve 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; (Pravilnik o kliničnem preskušanju)

  - "proces v katerem preizkušanec **prostovoljno** potrdi pripravljenost sodelovanja v kliničnem preskušanju, potem ko je bil **seznanjen z vsemi informacijami**, ki so pomembna za njegovo presojo o pripravljenosti vključitve v preskušanje. Svojo pripravljenost sodelovanja mora preizkušanec potrditi v obliki pisnega dokumenta s svojim podpisom in datuma privolitve;" (ICH Guidelines for Good Clinical Practice)

priprava → predstavitev → pisni pristanek

Zavestna in svobodna privolitev sodelujočih

- V procesu zavestne in svobodne privolite v klinično preskušanje mora biti kandidatom predstavljen na primeren in razumljiv način
  - namen raziskave
  - načrt raziskave
  - metode raziskave
  - predvidljive nevarnosti (neželeni učinki)
  - odškodnina v primeru okvare zdravja
  - varovanju osebnih podatkov
- Privolitev lahko kadar koli brez navedbe vzroka umaknejo
  - Zavrnitev ali preklic privolitve ne bo imela vpliva na primerno ali pravočasno medicinsko pomoč
  - pridobitev podpisa obrazca
- Zavestna in svobodna privolitev posebnih populacij

  (mladoletni, duševno nesposobni, bolniki v urgentnem stanju)
  - neposredna korist za njihov zdravje (znanstvena pomembno razumevanje bolezni?), raziskave ni mogoče delati na ljudeh sposobnih privolitve, minimalen obremenitve in nevarnosti
  - soglasje zakonitega varuha

Zavestna in svobodna privolitev sodelujočih

- Osnovna vsebina obrazca
  - Opis klinične raziskave – namen, trajanje, opis postopkov
  - Opis tveganja preizkušancev
  - Opis koristi preizkušancev (tistih, ki jih upravičeno pričakujemo)
  - Prikaz “alternativnih” načinov zdravljenja in njihovih slabosti/prednosti
  - Izjavo o zaupnosti podatkov
  - Za raziskave kjer je tveganje večje od minimalnega, je potrebno podati razlago o postopku zdravljenja, če pride do poškodb, ter o drugih nadomestil
  - Kontakti osebe na katero se lahko preizkušanci obrnejo, če imajo vprašanja v zvezi s raziskavo, pojavom neželene učinke...
  - Izjavo o prostovoljni udeležbi raziskave, zavrnitvi/preklicu sodelovanja brez izgube koristi do katerih imajo sicer pravico

Zavestna in svobodna privolitev sodelujočih

- Dodatna vsebina obrazca
  - Izjava o nepredvidljivih tveganjih kliničnega preskušanja za preizkušance (oz. plod pri nosečnicah)
  - Okoliščine v katerih raziskovalec zaključi sodelovanje preizkušanca v preiskavi (neglede na njegov prostovoljni pristanek)
  - Dodatne stroške za preizkušanca povezane z njegovo vključitve v raziskavo
  - Posledice predčasnega preklica sodelovanja
  - Izjavo o posredovanju vseh za zdravje pomembnih novih spoznanj posamezniku vključenem v raziskavo
  - Približno število preizkušancev vključenih v raziskavo

Zavestna in svobodna privolitev sodelujočih

- Primer I

Izjava o zavestni in svobodni privolitvi sodelujoče osebe v raziskavi

Spoštovani,

Raziskovalci IME USTANOVE ali USTANOV želimo izvesti raziskavo o učinkovitosti kombinacije prehranskih dopolnil (IME PREHRANSKEGA DOPOLNILA I in II) pri preprečevanju neželenih učinkov zdravljenja z antipsihotikom. Prehransko dopolnilo I je snov, ki organizem ščiti pred reaktivni spojinami. Prehranska dopolnila II je sestavni del XXX, poleg tega pa so prisotne v celičnih membranah, predvsem živčnih celic. Pri vaši bolezni, je lahko nastajanje poškodb močno povečano in zato običajen vnos preskušanih snovi s hrano ni zadosten. Posledično obramba ni ustrezna, kar lahko vodi do različnih neželenih pojavov.

Z vašo privolitvijo k sodelovanju v naši raziskavi boste poleg vaših obstoječih zdravil dvakrat na dan jemali tudi kapsule s kombinacijo prehranskih dopolnil. Dodatno zdravljenje bo trajalo 4 mesece. Na začetku in ob koncu raziskave vam bo odvzet vzorec krvi (20 ml) za laboratorijske raziskave. S pomočjo odvzetih vzorcev bo ovrednoten obseg poškodb, nivo obrambe telesa, določena bo koncentracija zdravila v krvi, z genetsko analizo pa bomo opredelili tudi vašo nagnjenost k poškodbam. Glavni cilj naše raziskave pa je ugotoviti ali dodatno zdravljenje z kombinacijo prehranskih dopolnil izboljša obstoječe zdravljenje. Jemanje prehranskih dopolnil ne predstavlja večjega tveganja za vaše zdravje.

V primeru, da imate kakršnokoli vprašanje v zvezi z raziskavo, smo Vam na voljo za dodatna pojasnila. Kontaktna oseba je (ime zdravnika) zdravnik, ki bo za vas skrbel v raziskavo. Dosegljiv je na telefosnki številki XXXX.

Iz raziskave ste lahko na vašo željo kadarkoli izključeni, vaše nesodelovanje v raziskavi pa v nobenem pogledu ne bo vplivalo na nadaljnjo zdravstveno obravnavo.

S podpisom tega lista potrjujete vašo zavestno in svobodno privolitev za sodelovanje v raziskavi.
Vaši osebni medicinski podatki bodo varovani.

NASLOV RAZSIKAVE
ŠIFRA RAZISKAVE

IZJAVA O ZAVESTNI IN SVOBODNI PRIVOLITVI ZA SODELOVANJE

Izjavljam, da sem seznanjen(a) s potekom raziskave in sem dobil(a) odgovore na vsa moja vprašanja.
Prejel(a) sem kopijo podpisane Izjave o zavestni in svobodni privolitvi za sodelovanje v raziskavi.

Preiskovanec(ka)

IME IN PRIIMEK PODPIS DATUM

Raziskovalec(ka)

IME IN PRIIMEK PODPIS DATUM

Zavestna in svobodna privolitev sodelujočih

- Primer II

STUDY NUMBER: _____

STUDY TITLE: Nitric Oxide Inhalation Therapy for Myocardial Ischemia in Patients with Coronary Artery Disease

INTRODUCTION

We invite you to take part in a research study.

First, we want you to know that

Taking part in [this] research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at [the institution] you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at [the medical institution] or with family, friends, or your personal physician or other health professional.

Purpose of Study

You have been diagnosed as having coronary artery disease, which is caused by atherosclerosis (build-up of cholesterol and scar tissue within the walls of arteries) and has affected segments of the large arteries of your heart. If atherosclerosis narrows the opening of the artery in a particular segment, blood flow may be limited, particularly during exercise or other stress. This can result in not enough oxygen in blood delivered to the heart muscle dependent upon that artery. As a result, you may experience shortness of breath and chest pain (angina pectoris) during your daily activities. You have previously received treatment for coronary artery disease with medications and with an attempt at revascularization, either by angioplasty or by surgery. Because you continue to be limited by chest pain so that even routine activities are difficult to accomplish, we invite you to volunteer for participation in a research study that is designed to determine whether inhalation of a gas (nitric oxide) mixed with room air may improve blood flow to your heart. Up to 25 patients with coronary artery disease will participate in this study.

The duration of this study is one month, with one week of inhalation of room air mixed with nitric oxide using a portable delivery device, and one week of room air alone from an identical-appearing delivery device, with two weeks separating the two treatment periods. You will not know, nor will we, the identity of the air mixture (that is, whether or not nitric oxide is present) in the delivery devices.

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However, the [specified person] will know at all times which air mixture you are breathing, and will also assign to you, by chance, the delivery device for your first treatment. However, you will receive the delivery device containing nitric oxide during one of the two treatment periods. Although we hope that you will complete both treatment periods of the study so that we can learn whether nitric oxide inhalation therapy can help patients like you, you are free to withdraw from the study at any time.

We will inform you of any significant findings discovered in the course of this study that might influence your decision to continue participation.

Description of Study

You have already undergone a heart scan that was performed during the previous year because of chest pain symptoms, and more recently a treadmill exercise test. Based on those results and lab work, you have been found eligible to participate in this study. We want to provide you with all the information you need, and answer all the questions you might have, before you sign this consent form and enroll in this study. During both of the one-week treatment periods, you will be hospitalized [in the study hospital] and you will continue your current medications throughout the entire study. You will be placed on a heart monitor so that we can follow your heart rate and rhythm throughout both treatment periods. We will measure your pulse, blood pressure, and breathing rate at least 3 times daily. We will also measure the oxygen in your blood by means of a clip device that fits over your finger. On the first day, you will exercise on a treadmill, just as was done to determine eligibility for the study, and ask you to tell us when you experience moderately uncomfortable chest pain (5 out of 10 in severity, with 10 being the worst chest pain you have experienced), at which point you will stop exercise. After that test, you begin the inhalation treatment with a small tank that you can carry with you and delivers a burst of air (with or without nitric oxide) through nasal prongs every time you inspire. If you have a cold and your nose is congested, we will postpone the treatment period until you can comfortably breathe through your nose. You will wear this device day and night, and remove it only to shower or bathe. You are free to walk around the nursing unit as you wish. If you commonly breathe through your mouth at night, as is often the case in persons who snore, the nasal prong delivery device cannot deliver air (with or without the nitric oxide) into your nose. This will cause a beeping sound on the monitor attached to the gas delivery system. If this happens with you at night, we will use instead of the nasal prongs a face mask attached with an elastic strap around your head. In this way, you will inhale the gas regardless of how you breathe.

At 2 hours and 24 hours after beginning inhalation therapy, we will draw a blood sample to make sure that there is no harm from breathing nitric oxide (this risk will be described later in the consent form).

On the morning of the second day, you will exercise once again on the treadmill, stopping when you experience moderately uncomfortable chest pain (5 out of 10 in severity). You will wear a face mask for gas delivery during this test.

On the morning of the 5th day additional electrodes will connect you to a monitor device that you carry with you as you walk around and records your heart rate and rhythm for 24 hours. You may be as active as you wish, including excursions off the nursing unit, but you must remain within the [medical institution].

On the morning of the 6th day, you will have a special echocardiogram with imaging of your heart during an infusion of dobutamine, a medicine that increases heart rate and contraction and serves to

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- Primer II

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stress the heart. This manner of stress testing is commonly used in hospitals around the country. Imaging your heart during stress can tell us whether the walls of the heart are receiving sufficient blood supply. The cardiologist performing this study will stop the dobutamine infusion either when you have reached a target heart rate (based on your age) or when you experience moderately uncomfortable chest pain (5 out of 10 in severity), just as was the case for the treadmill exercise tests. Your heart rate and rhythm will be continuously monitored during this study. You will wear a face mask for gas delivery during this test. That afternoon, you will undergo a magnetic resonance imaging (MRI) study of the blood flow in your heart and the contraction of your heart while receiving the same dosage of dobutamine as was used earlier in the day. At peak stress, an imaging agent called gadolinium will be injected into your vein in order to allow measurement of blood flow distribution within the heart. You will wear a face mask for gas delivery during this test.

On the morning of the 7th day, you will undergo another treadmill exercise test, stopping when you experience chest pain that is 5 out of 10 in severity, as before. You will wear a face mask for gas delivery during this test. Later that morning you will undergo a cardiac catheterization during which a long tube (catheter) will be placed into a vein of your neck, your arm, or your groin, depending on your preference and the physician's recommendation, after the skin has been numbed with xylocaine. This tube will be positioned within the right atrium of your heart and into a tubelike structure called the coronary sinus, where venous blood exits the heart muscle. A small catheter will be placed in an artery of your upper forearm after the skin has been numbed with xylocaine. Blood samples will be drawn through the tube in the heart and through the small tube in the artery at the beginning of the study and during infusion of dobutamine to stress your heart, using the same dose as was used in the previous day's stress studies. These blood samples will allow us to measure nitric oxide transported in your blood as well as measure levels of several substances that are important in atherosclerosis and that we believe might be reduced by nitric oxide. You will wear a face mask for gas delivery during this test.

After completing this week's worth of testing, you will go home for two weeks and then return to [the medical institution] for a week of identical testing with the alternate inhalation device to the one that you were assigned during the first week of the study. The total amount of blood required for this study is 300 cc (10 oz. or 20 tablespoons), which is two-thirds of the volume of blood donated by individuals to the Red Cross and to hospitals.

Explanation of the Procedures and Tests

1. *Nitric oxide administration.* Nitric oxide is a colorless, odorless gas which has been studied by us and other groups to determine whether this gas can dilate (enlarge) blood vessels of the lungs as well as the rest of the body. This gas is actually produced by the lining cells (endothelium) of healthy arteries, and keeps arteries dilated. However, production of this gas and the potency of this gas within arteries is markedly reduced in patients with atherosclerosis and coronary artery disease. Nitric oxide inhalation is approved by the U.S. Food and Drug Administration (FDA) for use in newborn infants with severe respiratory problems. Nitric oxide is also used on occasion to treat adults with severe respiratory problems in intensive care units, often for several weeks, without known complications from the gas itself. We have previously conducted studies in volunteer subjects with nitric oxide inhaled at 80 parts per million (80 molecules of nitric oxide per million molecules of air gases) without harm. The delivery system that you will be using delivers between 20 and 40 parts per million of nitric oxide mixed with

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room air. During those periods of time when you wear a face mask for gas delivery, the delivery of nitric oxide is set at 40 parts per million.

2. *Treadmill exercise testing.* The treadmill testing we will use for this study will be very familiar to you as it was important in determining your eligibility for the study. Your heart rhythm will be continuously monitored, as will your oxygen saturation using a finger clip device, and blood pressures will be measured approximately every 3 minutes. A nurse and a doctor will be in attendance throughout the study. In national statistics, the risk of a heart attack or death is approximately one in 10,000 exercise tests. The nurse and doctor are trained in the use of resuscitation equipment, which is kept next to the treadmill.

3. *Ambulatory monitoring.* Monitoring of your heart rate and rhythm will be done for 24 hours by having you wear a portable device with wires attached to sticky patches placed on your chest. Other than possible irritation of the skin, there is no risk to this test.

4. *Echocardiogram.* This test involves holding a small probe against the chest wall and allows the physician specialist to obtain pictures of the heart in order to assess the function of the various chambers of your heart. It uses sound waves to distinguish the various structures of the heart and does not involve any radiation. A small tube will be placed in the back of your hand or arm in order to give fluids into your vein, and to infuse dobutamine. This may cause a small bruise, and may cause you to feel briefly lightheaded and nauseated (faint). Echo measurements will be made before and during an infusion of dobutamine, which is a medicine commonly used in echocardiography laboratories around the country in order to stress the heart by increasing the heart rate and contractions. Imaging of the heart during this stress can help us determine whether sufficient blood flow is getting to heart muscle. The dobutamine will be infused until you experience moderately uncomfortable chest pain (5 out of 10 in severity) or until you achieve a standardized heart rate, based on your age. Some patients (less than 5 out of 100) experience headache, nausea, or anxiety during dobutamine testing. In national statistics, the risk of heart attack or serious heart rhythm problems requiring administration of medicines or an electroshock to the heart is approximately 3 out of 1,000 tests.

5. *Magnetic resonance imaging (MRI).* This test will provide pictures of the heart and measurement of blood flow in the heart during the administration of gadolinium. MRI does not use radiation, but instead uses the effects of magnets and radiowaves in order to provide pictures of the heart. On the day of the scan you will be taken to [the research institute] where the MRI instrument is located. After you arrive in the MRI area, you should use the bathroom before being placed in the machine, as the test can take about an hour. You will be asked to lie on a stretcher, which is inserted into a long, donut-shaped scanner that some people may find confining. The test is also quite noisy, but you can communicate through a microphone with the people performing the test. Your heart rate and blood pressure will be monitored during the study. If for any reason you feel that you cannot complete the MRI study, the scanning can be stopped and you can be removed immediately from the scanner. During the MRI examination you will receive an injection by vein of gadolinium. Gadolinium is approved by the FDA for the purposes of brightening areas of the heart, which we expect with increased blood flow to various areas of the heart. Experience with many thousands of patients here and elsewhere has shown that gadolinium is safe and without side effects in most patients. When side effects do occur (less than 5 out of 100 patients), they are usually mild and last for a short period of time. These include a feeling of coldness in the arm during the injection, headache, and nausea. More severe reactions (shortness of breath, wheezing, or lowering of blood pressure) have occurred in a small number of patients (fewer than 1 out of 100) and can be treated

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very easily. Some patients (less than 5 out of 100) describe a sensation of twitching in their legs that is caused by the stimulation of nerves of the extremities. In most cases this is not painful, but should it become painful to you, we can stop the study. At this time, there are no known health risks of MRI itself. However, there are certain medical conditions that can interfere with your MRI study and some can be hazardous. Therefore, in the interest of your safety, please tell us whether or not you have any of the following items in your body:

Artificial heart valve	Yes _____	No _____
Cardiac pacemaker	Yes _____	No _____
Automatic implantable defibrillator (AICD)	Yes _____	No _____
Neural pacemaker	Yes _____	No _____
Aneurysmal clips on arteries on the brain	Yes _____	No _____
Shrapnel	Yes _____	No _____
Foreign bodies in the eye (e.g. metal shavings)	Yes _____	No _____
Surgical clips	Yes _____	No _____

You may have had placement of a stent within one or more arteries of your heart. MRI is safe in patients with stents, although we require that at least 6 months elapse from the time that the stents were placed.

6. *Cardiac catheterization.* This test involves inserting small tubes into the artery of the arm and a long tube into the venous side of the heart by way of an arm or neck vein after numbing the skin with xylocaine, so that blood samples can be obtained before and during the infusion of dobutamine. There is a small (1 in 500) chance of injury to the right side of the heart, which could result in leakage of blood out of the heart and into the sac (pericardium) in which the heart is located. If this happens and if your blood pressure falls because the heart is compressed by blood in the sac, a needle will be inserted under the rib cage to draw the blood out. There is a less than 1 out of 100 chance of puncturing the lung, requiring placement of a chest tube to remove the excess air. Placement of the tube into the heart requires about two minutes of x-ray exposure. The radiation exposure from the two cardiac catheterizations required during the study is for research purposes only, totalling 1.26 rem to the skin, 0.146 rem to the heart, and 0.125 rem to the left lung. This radiation exposure is less than the 13-week (3 rem) radiation dose to each tissue of the body usually permitted to adult research subjects at [the research institute], and less than the 5 rem limit allowed per year for research purposes. Please tell us if you have participated in other research studies, here or elsewhere, so that we may make sure that your total radiation exposure from all studies is not too much. The [safety staff of the research institute], a group of experts on radiation safety matters, has reviewed the use of radiation in this study and has approved the use as necessary to obtain the research information desired. Potential long-term risks from the radiation doses used in this study are uncertain, but these doses to date have not been associated with any definite adverse effects. Thus, the risk to you at this time is estimated to be slight.

Risks

The risks associated with treadmill exercising testing, echo testing with dobutamine stress, MRI scanning with dobutamine stress, and cardiac catheterization with dobutamine stress have been discussed previously in this consent form. Thus, in this section we will discuss the risk associated with the treatment that is the focus of our study, nitric oxide inhalation.

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To the best of our knowledge, nitric oxide has not been administered as a gas to patients with coronary artery disease or other forms of cardiovascular disease. However, nitric oxide has been used in normal volunteers and in patients for several years and without harm. At 20-40 parts per million, the dose that you will be given for a week, inhaled nitric oxide rarely (less than 1 in 1,000) causes adverse effects. Some of the possible adverse effects include bronchospasm (rapid contraction and relaxation of the muscles around your breathing tubes) and pulmonary edema (fluid in the lungs). We will minimize the likelihood of such adverse effects by properly caring for the equipment used to deliver the nitric oxide. At high doses, inhaled nitric oxide can react with oxygen in your red blood cells, forming methemoglobin. *High levels of methemoglobin can be dangerous because of the inability of this molecule* to transport oxygen in blood. Methemoglobin formation is not expected to be a problem at the dose of nitric oxide you will receive for one week. During our previous studies with normal volunteers and patients with sickle cell anemia, methemoglobin was no greater than 1% of all hemoglobin when nitric oxide was administered at 80 parts per million for approximately 3 hours. In published studies of patients with pulmonary disease receiving nitric oxide for several weeks, no elevation in methemoglobin greater than 2% has been reported. We will measure your methemoglobin at 2 hours and at 24 hours during the treatment phases of the study to ensure that the levels are maintained at a safe range less than 2% of total hemoglobin. If methemoglobin levels exceed 2% of the total hemoglobin, we will stop your participation in the study. Also, we will monitor the oxygen saturation of your blood throughout the week by means of a device that fits on your finger. If we see any harmful effect of nitric oxide on your blood pressure, heart rhythm, breathing, or oxygen saturation of your blood, we will stop your participation in the study. There is also a possibility that nitric oxide gas combined with nitroglycerin (a drug that releases nitric oxide into blood vessels) may have additive effects, which could lower blood pressure and cause you to feel lightheaded or have chest pain. For this reason, we will monitor your blood pressure and heart rate frequently after beginning the gas therapy. Further, we will give you a standard dose of nitroglycerin to take under the tongue while you are using the gas therapy in order to be sure that your blood pressure does not fall to such a level that you feel lightheaded or feel chest pain. If you should feel these symptoms with a fall in blood pressure, we will stop your participation in the study. During those periods of time when you must wear a face mask, you may experience some irritation (redness and itching) where the face mask comes in contact with skin. The effects of nitric oxide inhalation on blood glucose levels are not known, and may cause fluctuations of blood sugar levels in patients with diabetes mellitus. If you are diabetic, we will obtain blood sugar levels each morning and afternoon, and make adjustments in your diabetes medication if necessary. This may require the occasional administration of insulin by injection while you are undergoing testing, even if you are only taking pills for blood sugar control.

Benefits

Based on what we know about nitric oxide in studies performed in animals and in humans, we believe that nitric oxide may benefit your heart disease by improving blood flow to the heart muscle during stress. However, it is possible that nitric oxide either does not help the heart or that the number and location of atherosclerotic blockages in the arteries in your heart are too severe for nitric oxide to be of benefit. Based on our experience to date and that of other physicians and scientists who have studied nitric oxide, we do not believe that nitric oxide will harm you. However, we will watch you very closely on our inpatient ward while you use the inhalation device to maximize the safety in this study. Your safe

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participation is also ensured by maintaining the medications that you were taking prior to enrollment. As an alternative to participating in this study, you may be able to undergo additional angioplasty or surgical revascularization procedures. Also, there are other experimental procedures being performed at other medical centers, including injection or infusion into the heart of substances [that] may grow new blood vessels, and laser treatment of heart muscle to create new blood vessels. It may not be possible to supply you with nitric oxide gas for continued inhalation therapy after you complete the study, as use of this approach to treatment of patients like you has not been approved by the FDA, the government agency responsible for approval and supervision of drug therapies. However, should this study prove the benefit and safety of nitric oxide inhalation therapy for patients with coronary artery disease, this therapy may possibly be available in the future.

Confidentiality

The Federal Privacy Act protects the confidentiality of your medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, [the study sponsor] or their representative, or other authorized people.

Monetary Compensation

You will receive payment for the inconvenience and time spent on our inpatient ward during the study. Compensation includes $200 for each of the one-week treatment periods in the [medical institution]. Furthermore, you will receive an additional $100 for completing the study. Thus, a total of $500 of compensation will be given to you upon completion of the study.

Patient Representative

If you have further questions or concerns regarding your participation in this research study, you may contact the patient representative.

[A consent form for non-study-related intervention was omitted—eds.]

OTHER PERTINENT INFORMATION

1. *Confidentiality.* When results of [a medical] study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the [research staff] will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the [research staff] will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

2. *Policy Regarding Research-Related Injuries.* The [medical institution] will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the [medical institution]. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

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STUDY NUMBER: _____

3. *Payments.* The amount of payment to research volunteers is guided by the [medical institution guidelines]. In general, patients are not paid for taking part in research studies at the [medical institution].

4. *Problems or Questions.* If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, [name (telephone number)].

Other researchers you may call are [_____].

You may also call the [medical institution's] patient representative at [telephone number].

5. *Consent Document.* Please keep a copy of this document in case you want to read it again.

Complete Appropriate Items Below:

A. Adult Patient's Consent
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

_____ _____
Signature of Adult Patient/Legal Representative Date

B. Parent's Permission for Minor Patient
I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

_____ _____
Signature of Parent(s)/Guardian Date

C. Child's Verbal Assent (If Applicable)
The information in the above consent was described to my child, and my child agrees to participate in the study.

_____ _____
Signature of Parent(s)/Guardian Date

This consent document has been approved for use from _____ to _____
[applicable dates]

_____ _____ _____ _____
Signature of Investigator Date Signature of Witness Date

Prijava kliničnega preskušanja na Komisijo za klinična preskušanja (KKP)

Pravilnik o kliničnem preskušanju – 19. in 20 člen:

- Odobritev kliničnega preskušanja zdravila je treba pridobiti, kadar se bo preskušanje izvajalo:

1. z zdravili za gensko zdravljenje;
2. z zdravili za zdravljenje s somatskimi ali ksenogenimi celicami,
3. z zdravili, ki vsebujejo gensko spremenjene organizme.

- Priglasitev kliničnega preskušanja zdravila je potrebna v vseh ostalih primerih, ki niso navedeni v prejšnjem odstavku.

- Odobritev ali priglasitev kliničnega preskušanja zdravila ni potrebna za ne-intervencijsko klinično preskušanje.

Prijava kliničnega preskušanja na Komisijo za klinična preskušanja (KKP)

- Ne-intervencijsko klinično preskušanje
  - je klinično preskušanje zdravila pri katerem izbira bolnikov, način zdravljenja, izbor zdravila, predpisovanje zdravila, določitev preiskav in spremljanje bolnika ne odstopa od ustaljenega načina zdravljenja
- če preizkušena 'snov' ustreza definiciji zdravila in če preskušanje ustreza definiciji kliničnega preskušanja, moramo biti za KP podana vloga za odobritev ali priglasitev
  - Zdravilo je vsaka snov ali kombinacija snovi, ki so predstavljene z lastnostmi za zdravljenje ali preprečevanje bolezni ljudi ali živali. ...
  - Klinično preskušanje zdravil za uporabo v humani medicini je raziskava na zdravih in bolnih ljudeh, ki ima namen odkriti ali potrditi klinične, farmakološke ali druge farmakodinamske in farmakokinetične učinke zdravil v preskušanju ali odkriti neželene učinke zdravila v preskušanju ali proučiti absorpcijo, porazdelitev, presnovo in izločanje zdravila v preskušanjem, s ciljem dokazati njegovo varnost, ali učinkovitost.

Prijava kliničnega preskušanja na Komisijo za klinična preskušanja (KKP)

- Intervencijsko/ neintervencijsko klinično preskušanje - algoritem

IS IT A CLINICAL TRIAL OF A MEDICINAL PRODUCT?

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions contact the clinical trials unit of your competent authority.

A	B	C	D	E
A CLINICAL TRIAL OF A MEDICINAL PRODUCT?				A NON-INTERVENTIONAL CLINICAL TRIAL?
Is it a medicinal product (MP)?[i]	**Is it not a medicinal product?**	**What effects of the medicine are you looking for?**	**Why are you looking for those effects?**	**How are you looking for those effects?**
If you answer no to all the questions in column A, the activity is not a clinical trial on a MP. If you answer yes to any of the questions below go to column B.	If you answer yes to the question below in column B the activity is not a clinical trial on a MP. If you answer no to this question below go to column C.	If you answer no to all the questions in column C the activity is not a clinical trial under the scope of Directive 2001/20/EC. If you answer yes to any of the questions below go to column D.	If you answer no to all the questions in column D the activity is not a clinical trial under the scope of Directive 2001/20/EC. If you answer yes to any of the questions below go to column E.	If you answer yes to all these questions the activity is a non-interventional trial which is outside the scope of Directive 2001/20/EC. If your answers in columns A,B,C & D brought you to column E and you answer no to any of these questions the activity is a clinical trial within the scope of the Directive.
A.1 Is it a substance[ii] or combination of substances presented as having properties for treating or preventing disease in human beings ? A.2 Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose? A.3 Is it an active substance in a pharmaceutical form?	B.1 Are you only administering any of the following substances? • Human whole blood[iii]; • Human blood cells; • Human plasma; • Tissues except a somatic cell therapy medicinal product[iv]; • A food product[v] (including dietary supplements) not presented as a medicine; • A cosmetic product[vi] • A medical device	C.1 To discover or verify/compare its clinical effects? C.2 To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics? C.3 To identify or verify/compare its adverse reactions? C.4 To study or verify/compare its absorption, distribution, metabolism or excretion?	D.1 To ascertain or verify/compare the efficacy[vii] of the medicine? D.2 To ascertain or verify/compare the safety of the medicine?	E.1 Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned? E.2 Are the products prescribed in the usual manner in accordance with the terms of that authorisation? E.3 Does the assignment of any patient involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol[viii]? E.4 Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study? E.5 Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice? E.6 Will epidemiological methods be used for the analysis of the data arising from the study?

Priprava vloge KKP

- **Vsebina vloge:**

1. **spremni dopis**. Kadar vlogo v imenu sponzorja predloži pooblaščenec, mora predložiti pooblastilo sponzorja;

2. **izpolnjen in podpisan enoten evropski obrazec** za odobritev oziroma priglasitev kliničnega preskušanja zdravila. Obrazec je priloga priporočil iz prejšnjega odstavka in je dostopen na spletni strani Evropske agencije za vrednotenje zdravil (v nadaljnjem besedilu: EMEA). Izpolnjen obrazec mora predlagatelj predložiti tudi v elektronski obliki, kot XML datoteko.

   http://dg3.eudra.org

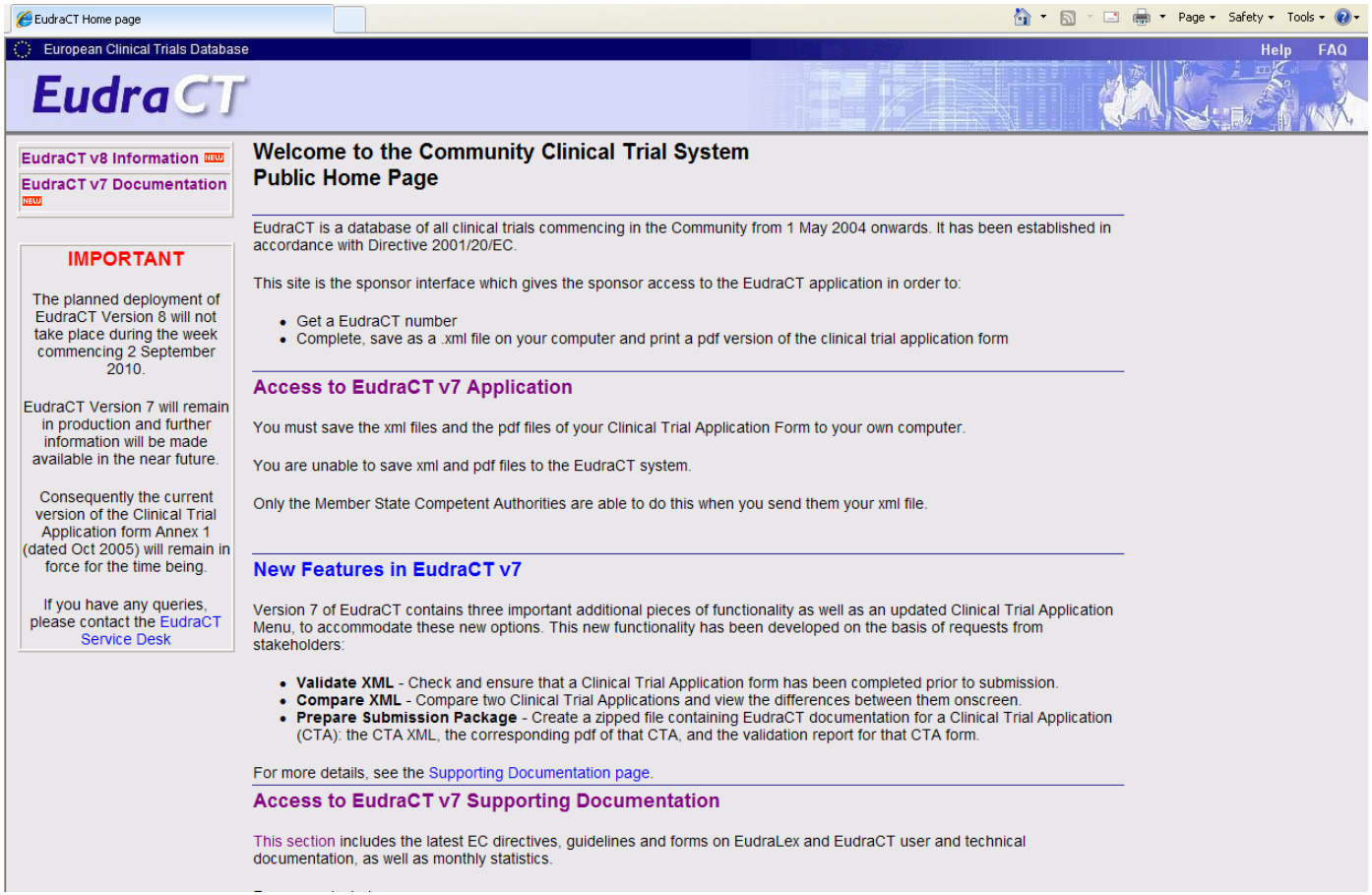
   ali spletna stran EMEA-e:

   http://www.emea.eu.int),

Priprava vloge KKP

- **EudraCT:**

Enoten evropski obrazec za odobritev oziroma priglasitev kliničnega preskušanja zdravila – osnovna stran

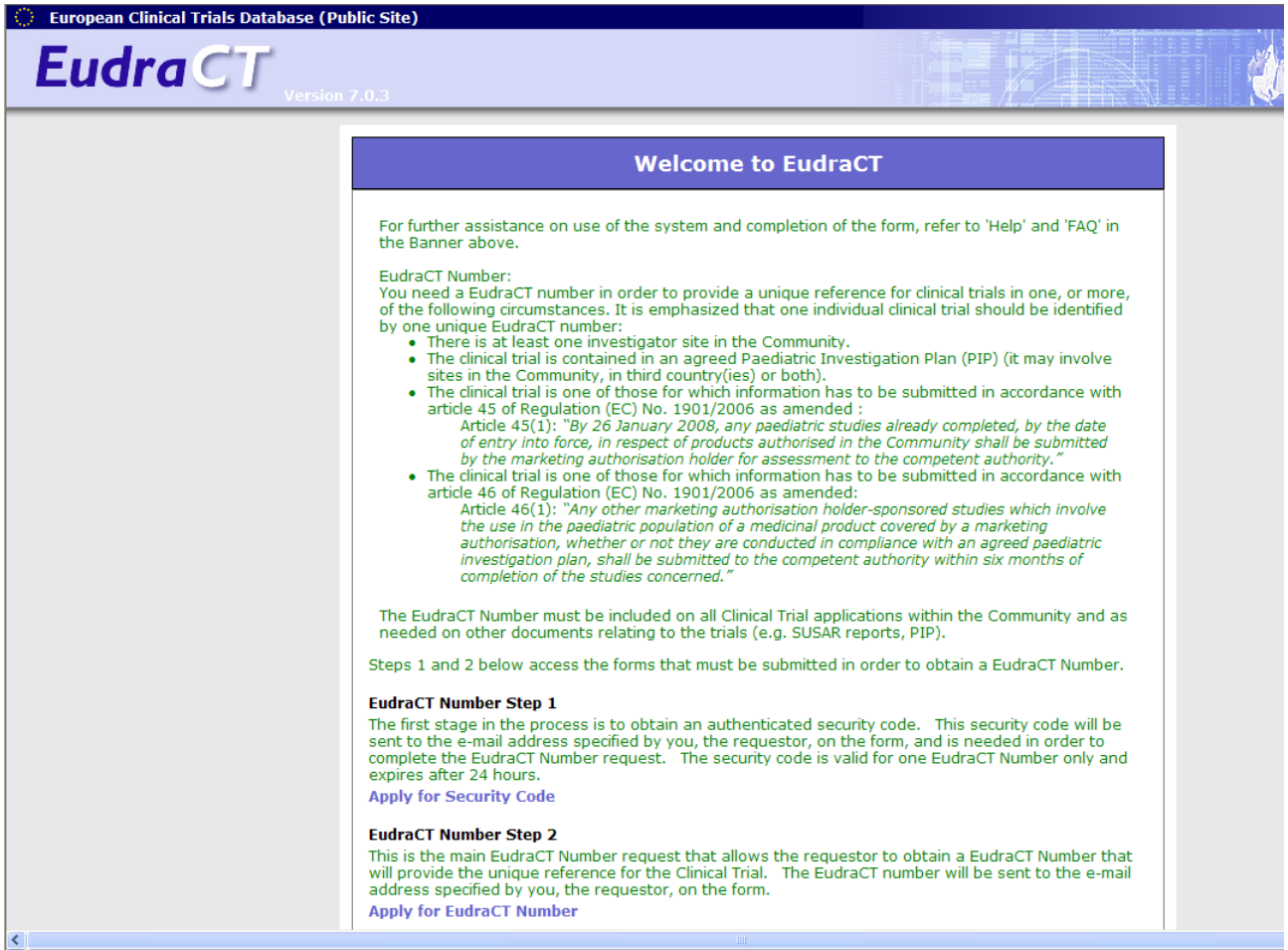


Priprava vloge KKP

- **EudraCT:**

Faze izpolnjevanja obrazca: 1. Varnostna koda - Apply for Security Code

2. EudraCT številka - Apply for EudraCT Number

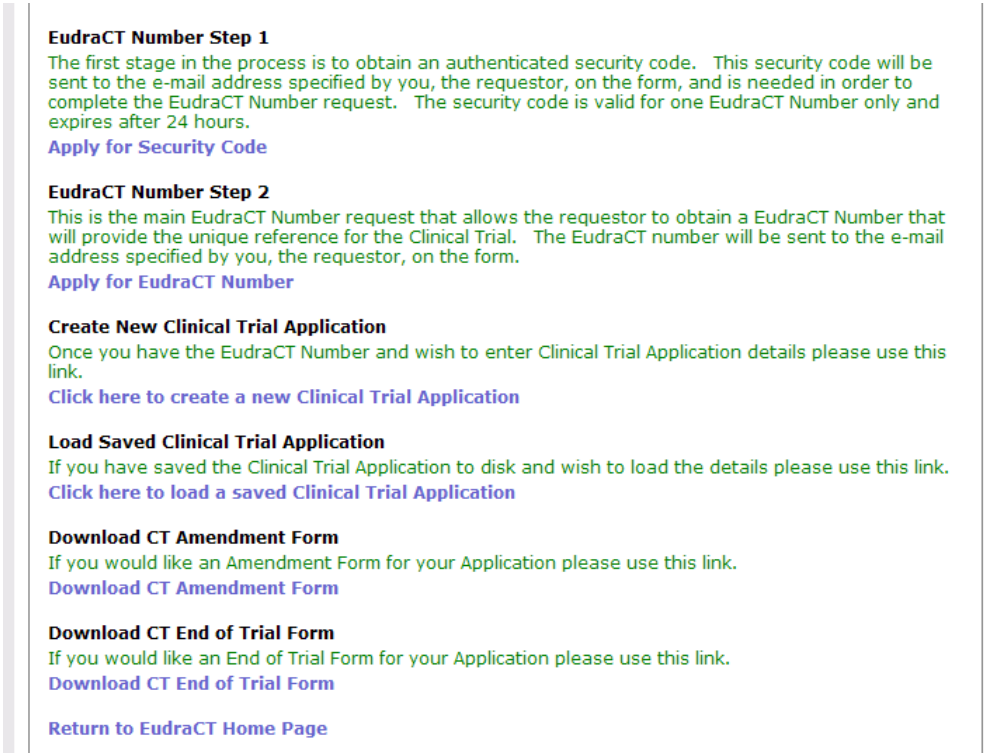


Priprava vloge KKP

- **EudraCT:**

Faze izpolnjevanja obrazca:

3. Nova aplikacija kliničnega preskušanja – Create New Clinical Trial Application



EudraCT Number Step 1

The first stage in the process is to obtain an authenticated security code. This security code will be sent to the e-mail address specified by you, the requestor, on the form, and is needed in order to complete the EudraCT Number request. The security code is valid for one EudraCT Number only and expires after 24 hours.

Apply for Security Code

EudraCT Number Step 2

This is the main EudraCT Number request that allows the requestor to obtain a EudraCT Number that will provide the unique reference for the Clinical Trial. The EudraCT number will be sent to the e-mail address specified by you, the requestor, on the form.

Apply for EudraCT Number

Create New Clinical Trial Application

Once you have the EudraCT Number and wish to enter Clinical Trial Application details please use this link.

Click here to create a new Clinical Trial Application

Load Saved Clinical Trial Application

If you have saved the Clinical Trial Application to disk and wish to load the details please use this link.

Click here to load a saved Clinical Trial Application

Download CT Amendment Form

If you would like an Amendment Form for your Application please use this link.

Download CT Amendment Form

Download CT End of Trial Form

If you would like an End of Trial Form for your Application please use this link.

Download CT End of Trial Form

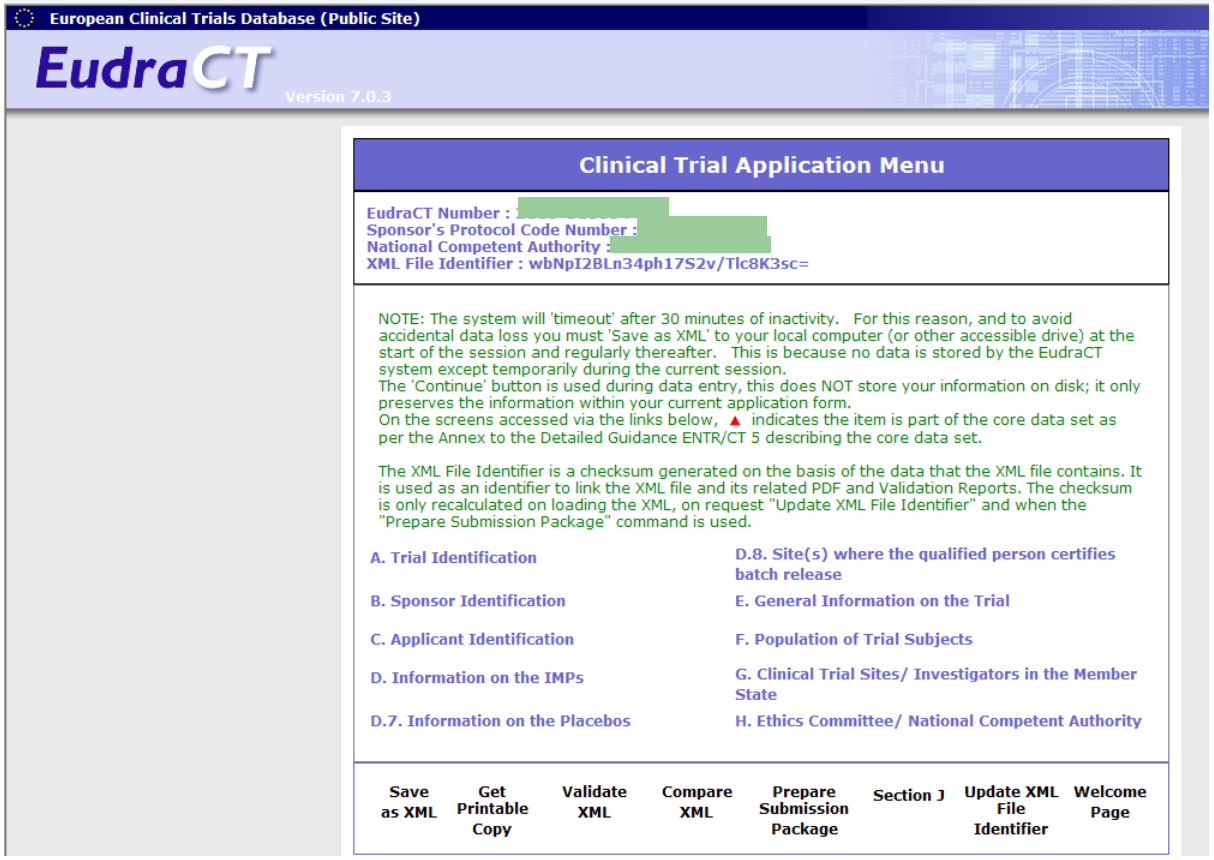
Return to EudraCT Home Page

Priprava vloge KKP

- **EudraCT:**

Faze izpolnjevanja obrazca:

4. Izpolnjevanje enotnega evropskega

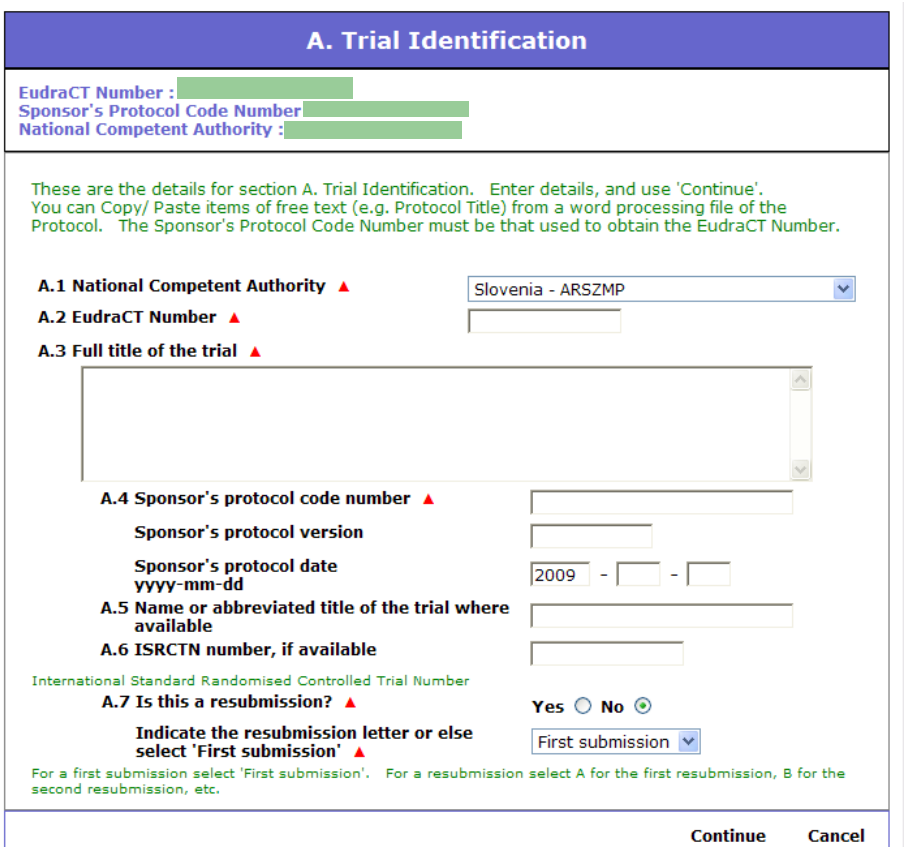


Priprava vloge KKP

- **EudraCT:**

Faze izpolnjevanja obrazca:

4.1. Izpolnjevanje enotnega evropskega – podatki v zvezi s kliničnem preskušanjem

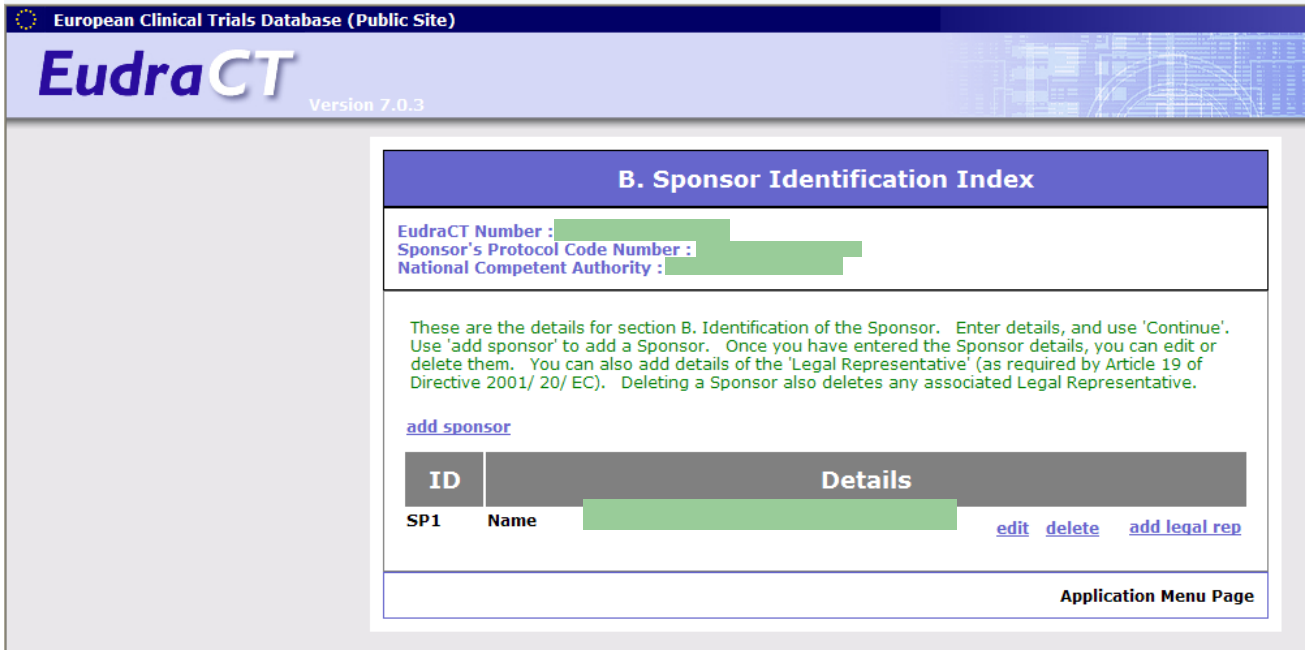


Priprava vloge KKP

- **EudraCT:**

Faze izpolnjevanja obrazca:

4.2. Izpolnjevanje enotnega evropskega – podatki v zvezi s sponzorjem



Priprava vloge KKP

- **EudraCT:**

Faze izpolnjevanja obrazca:

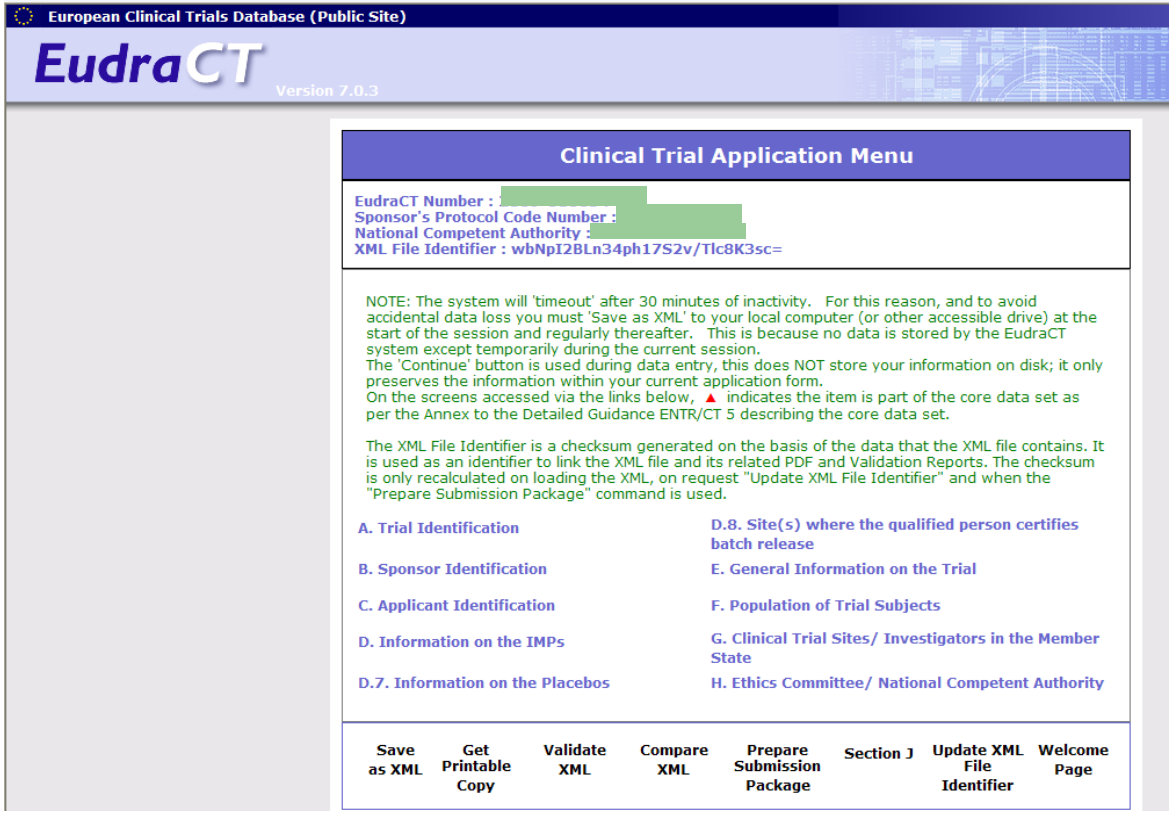
4.3. Izpolnjevanje enotnega evropskega – prijava JAZMP ali KME

Priprava vloge KKP

- **EudraCT:**

Faze izpolnjevanja obrazca:

4.4 Izpolnjevanje enotnega evropskega – zdravilo, placebo, izdelava zdravila/placebo, splošne informacije, populacija preizkušancev, klinične ustanove, KME in JAZMP-KKP



Priprava vloge KKP

- **Vsebina vloge (nadaljevanje):**

3. **protokol preskušanja**, ki ga morata podpisati sponzor in glavni raziskovalec oziroma raziskovalec koordinator v primeru multicentričnega kliničnega preskušanja;
4. **brošuro za raziskovalca**

   (podatki o analiznem, farmakološko-toksikološkem in o že opravljenem kliničnem preskušanju zdravila, ki so pomembni za zadevno klinično preskušanje zdravila)
5. **dosje o zdravilu v preskušanju** (IMPD):

   a. celoten dosje o zdravilu predlagatelj predloži, kadar organu, pristojnemu za zdravila, prvič posreduje podatke o zdravilu v kliničnem preskušanju;

   b. skrajšan dosje o zdravilu predlagatelj predloži, kadar je zdravilo v kliničnem preskušanju že pridobilo dovoljenje za promet v katerikoli državi članici Evropske unije oziroma je organ, pristojen za zdravila pridobil podatke o zdravilu iz drugega kliničnega preskušanja zdravila;

   c. povzetek glavnih značilnosti zdravila, kadar klinično preskušanje zdravila ne presega okvirov tega povzetka;

Priprava vloge KKP

- **Vsebina vloge (nadaljevanje):**

6. **povzetek protokola** preskušanja v petih izvodih v slovenskem jeziku;
7. **seznam držav**, v katerih je sponzor že dal vlogo za isto klinično preskušanje zdravila;
8. **mnenje Nacionalne komisije za medicinsko etiko**. Kadar postopek za odobritev oziroma priglasitev kliničnega preskušanja zdravila poteka vzporedno, mora predlagatelj predložiti mnenje Nacionalne komisije za medicinsko etiko takoj, ko je to na voljo;
9. **dovoljenje za izdelavo zdravila**, kadar je zdravilo v kliničnem preskušanju izdelano v Evropski uniji;
10. **dovoljenje za uvoz v Evropsko unijo** in izjavo odgovorne osebe, da poteka proizvodnja v skladu s standardi dobre proizvodne prakse, kadar je zdravilo v kliničnem preskušanju izdelano v tretjih državah;

Priprava vloge KKP

- **Vsebina vloge (nadaljevanje):**

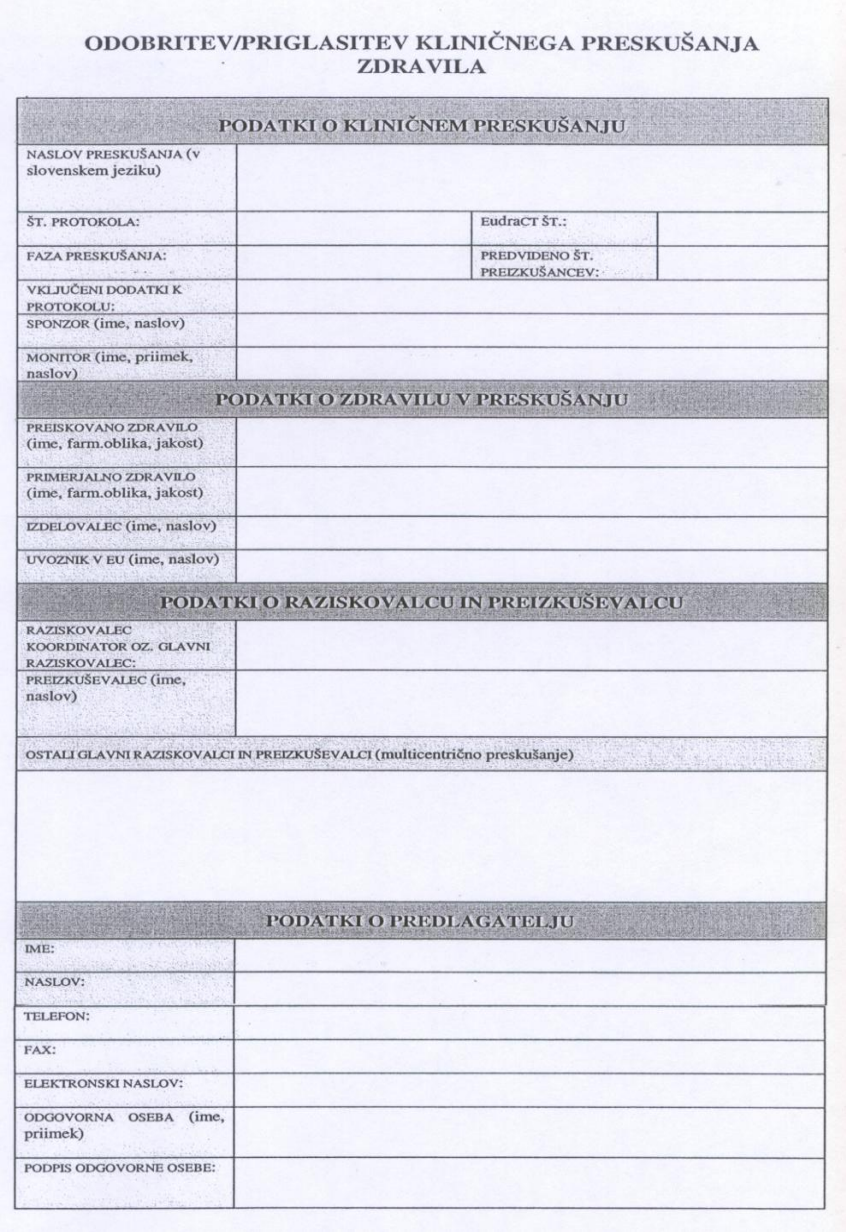
11. **kratek življenjepis glavnega raziskovalca**, odgovornega za izvajanje kliničnega preskušanja zdravila na posameznem mestu preskušanja;
12. **dokazilo o zavarovanju odškodninske odgovornosti** sponzorja za primer morebitne škode za preizkušanca, nastale kot posledica kliničnega preskušanja zdravila;
13. **obrazec pisne privolitve preizkušanca** in besedilo, s katerim bodo preizkušanci predhodno obveščeni o namenu kliničnega preskušanja zdravila in o morebitnih tveganjih za njihovo zdravje (v slovenskem in angleškem jeziku);
14. **izpolnjen obrazec KLPR-A** s podatki o kliničnem preskušanju zdravila, ki ga mora predlagatelj predložiti tudi v elektronski obliki, kot Word datoteko. Obrazec KLPR-A je dostopen na spletni strani organa, pristojnega za zdravila (http://www2.gov.si/mz/mz-splet.nsf);

Priprava vloge KKP

- **Vsebina vloge (nadaljevanje):**

14. **izpolnjen obrazec KLPR-A**

- Podatki o kliničnem preskušanju



ODOBRITEV/PRIGLASITEV KLINIČNEGA PRESKUŠANJA ZDRAVILA

PODATKI O KLINIČNEM PRESKUŠANJU			
NASLOV PRESKUŠANJA (v slovenskem jeziku)			
ŠT. PROTOKOLA:		EudraCT ŠT.:	
FAZA PRESKUŠANJA:		PREDVIDENO ŠT. PREIZKUŠANCEV:	
VKLJUČENI DODATKI K PROTOKOLU:			
SPONZOR (ime, naslov)			
MONITOR (ime, priimek, naslov)			
PODATKI O ZDRAVILU V PRESKUŠANJU			
PREISKOVANO ZDRAVILO (ime, farm.oblika, jakost)			
PRIMERJALNO ZDRAVILO (ime, farm.oblika, jakost)			
IZDELOVALEC (ime, naslov)			
UVOZNIK V EU (ime, naslov)			
PODATKI O RAZISKOVALCU IN PREIZKUŠEVALCU			
RAZISKOVALEC KOORDINATOR OZ. GLAVNI RAZISKOVALEC:			
PREIZKUŠEVALEC (ime, naslov)			
OSTALI GLAVNI RAZISKOVALCI IN PREIZKUŠEVALCI (multicentrično preskušanje)			
PODATKI O PREDLAGATELJU			
IME:			
NASLOV:			
TELEFON:			
FAX:			
ELEKTRONSKI NASLOV:			
ODGOVORNA OSEBA (ime, priimek)			
PODPIS ODGOVORNE OSEBE:			

Priprava vloge KKP

- **Vsebina vloge (nadaljevanje):**

15. **izjavo glavnega raziskovalca,** na **obrazcu KLPR-B**, ki je dostopen na spletni strani organa, pristojnega za zdravila;

IZJAVA GLAVNEGA RAZISKOVALCA/ GLAVNE RAZISKOVALKE	
IME, PRIIMEK, NAZIV:	
STROKOVNA USPOSOBLJENOST:	
TELEFON:	
ELEKTRONSKI NASLOV:	
IZJAVA	
SEZNANJEN/A SEM Z NEKLINIČNIMI IN KLINIČNIMI LASTNOSTMI ZDRAVILA V PRESKUŠANJU, KI JIH JE PREDSTAVIL SPONZOR TER Z NAMENOM PRESKUŠANJA. PRESKUŠANJE BO POTEKALO PO PREDLOŽENEM PROTOKOLU, PO NAČELIH DOBRE KLINIČNE PRAKSE, HELSINŠKE DEKLARACIJE IN VELJAVNE ZAKONODAJE.	
DATUM:	
PODPIS:	

Priprava vloge KKP

- **Vsebina vloge (nadaljevanje):**

16. **soglasje odgovorne osebe preskuševalca** (direktorja, predstojnika) k imenovanju glavnega raziskovalca ter uporabi prostorov, kadrov in opreme pri izvajanju kliničnega preskušanja zdravila na **obrazcu KLPR-C**, ki je dostopen na spletni strani organa, pristojnega za zdravila;

IZJAVA ODGOVORNE OSEBE PRESKUŠEVALCA	
IME ORGANIZACIJE:	
NASLOV:	
TELEFON:	
FAX:	
ELEKTRONSKI NASLOV:	
ODGOVORNA OSEBA (ime, priimek, naziv):	
STRINJAM SE, DA KLINIČNO PRESKUŠANJE Z NASLOVOM:	
GLAVNI RAZISKOVALEC:	
SPONZOR:	
POTEKA V PROSTORIH PREŠKUŠEVALCA, DA BODO POTREBNA OPREMA IN KADRI NA VOLJO GLAVNEMU RAZISKOVALCU TER, DA BO OMOGOČEN NEMOTEN NADZOR POTEKA PRESKUŠANJA S STRANI SPONZORJA IN ORGANA, PRISTOJNEGA ZA ZDRAVILA.	
DATUM:	
PODPIS ODGOVORNE OSEBE:	

Priprava vloge KKP

- **Vsebina vloge (nadaljevanje):**

17. **osnutek označevanja zdravila** v kliničnem preskušanju v slovenskem jeziku;
18. **ostale dokumente** v skladu s priporočili Evropske unije iz prvega odstavka 20. člena tega pravilnika, v njihovem vsakokrat veljavnem besedilu, kadar je to potrebno;
19. **dokazilo o plačilu stroškov postopka**;
20. **predpisano upravno takso**;

Osnovni vsebini vlog za KKP in KME

KKP	KME
1. spremni dopis	1. Splošne informacije
2. Obrazec EudraCT	2. Opis klinične preiskave
3. Protokol preskušanja	3. Opis tveganja/koristi za preizkušance
4. brošuro za raziskovalca	4. Izjavo o zaupnosti podatkov
5. dosje o zdravilu	5. Kontakti osebe odgovorne za preizkušance
6. povzetek protokola	6. Izjavo o prostovoljni udeležbi raziskave
7. Seznam držav s prijavo	
8. Mnenje KME	
9. Dovoljenje za izdelavo zdravila	
10. Dovoljenje za uvoz zdravila	
11. CV glavnega raziskovalca	
12. Zavarovanje	
13. Izjavo o prostovoljni udeležbi razsikave	
14. KLRP-A, B, C	
15. Osnutek označevanja	
16. Plačilo stroškov postopka + upravna taksa	

Na osnovi vprašalnika oblikujete enostaven primer izjave prostovoljnega pristanka:

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