XV Nedelja bolničke kliničke farmakologije 23-24. decembar 2023.

Sekcija za kliničku farmakologiju “dr Srdjan Djani Marković”
Srpsko lekarsko društvo

ZDRAVI DOBROVOLJCI U KLINIČKIM STUDIJAMA

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Prva primena novih supstanci na ljudima (FIH studije)

Ciljevi FIH studija:

- klinička farmakologija
- FK, FD
- podnošljivost i bezbednost
- translacija pretkliničkih efekata na ljude

Investigational Medicinal Product (IMP) = IND
ispitivani medicinski proizvod

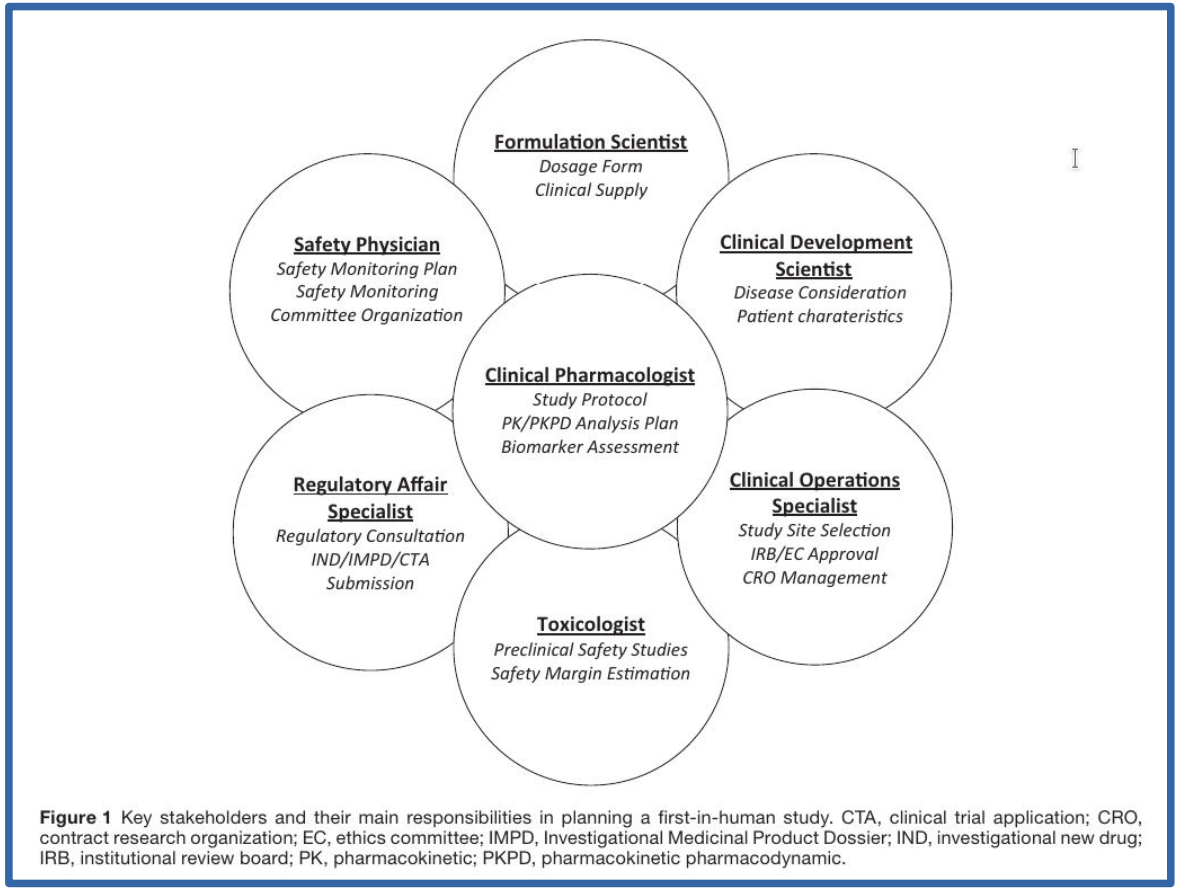


Figure 1 Key stakeholders and their main responsibilities in planning a first-in-human study. CTA, clinical trial application; CRO, contract research organization; EC, ethics committee; IMPD, Investigational Medicinal Product Dossier; IND, investigational new drug; IRB, institutional review board; PK, pharmacokinetic; PKPD, pharmacokinetic pharmacodynamic.

EMEA/CHMP/SWP/28367/07 Rev. 1, 20 July 2017
Clin Transl Sci 2019; 12: 6–19

На основу члана 78. став 3. Закона о лековима и медицинским средствима („Службени гласник РС”, бр. 30/10, 107/12, 105/17 – др. закон и 113/17 – др. закон),

министар здравља доноси

ПРАВИЛНИК
О ИЗМЕНАМА И ДОПУНИ ПРАВИЛНИКА О КЛИНИЧКОМ ИСПИТИВАЊУ ЛЕКОВА У ХУМАНОЈ МЕДИЦИНИ

Члан 1.

У Правилнику о клиничком испитивању лекова у хуманој медицини („Службени гласник РС”, број 51/22 и 65/23), у члану 2. став 1. тачка 23), члану 6. став 1. тач. 29) и 31), члану 25, члану 26. став 1. тачка 3), члану 38. ст. 1. и 2, члану 39. ст. 1. и 3, члану 41. и члану 44. став 3. речи: „у јавној својини” бришу се.

Члан 2.

У члану 4. став 2. тачка 12) мења се и гласи:

„12) фазе испитивања (I, Ia, Ib, II, IIa, IIb, III, IIIa, IIIb, IV),”.

После става 6. додаје се став 7. који гласи:

„Фазе испитивања I, Ia и Ib могу да се спроводе само у здравственој установи у јавној својини.”

Члан 3.

У члану 30. став 1. речи: „у јавној својини” замењују се речима: „са пуним радним временом на неодређено време односно чији је радноправни статус у здравственој установи у јавној својини утврђен у складу са споразумом из члана 157. став 4. Закона о здравственој заштити („Службени гласник РС”, број 25/19)”.

Zdravi dobrovoljci

Definicija zdravog dobrovoljca:

- zdravstveni status
- morfološke karakteristike
- mentalna sposobnost

NIH: a healthy volunteer is “someone with no known significant health problems who participates in research to test a new drug, device, or intervention”.

Svake godine – 3500 zdravih dobrovoljaca u NIH studijama

Eur J Clin Pharmacol 2017; 73: 409–16
https://trialx.com/i-was-broke-so-i-signed-up-for-a-clinical-study-my-clinical-trial-experience/

Zdravi dobrovoljci

Table. 1 Time windows for screening examinations

First-in-human trials	•Check laboratory values and inclusion/exclusion criteria within 3 days prior to first dosing •If screening performed earlier than 3 days prior to first dosing, repeat laboratory assessments and check whether relevant changes/important events occurred
Trials with 'clinically established IMPs' (e.g. bioequivalence trials for generic medicines applications)	•Screening examination usually between −21 and −1 days prior to first dosing; take risk-adapted approach

IMP investigational medicinal product

Eur J Clin Pharmacol 2017; 73: 409–16

Zdravi dobrovoljci

Table. 2 Heart/pulse rate—normal ranges/clinically acceptable ranges

First-in-human trials	•Range between 50 and 90 bpm is recommended • Some stakeholders consider heart/pulse rate <50 and ≥45 bpm acceptable in case of normal thyroid function (medical history, physical examination, normal TSH) and no signs of diseases associated with bradycardia plus, if required, normal cardiological examination (including echocardiography and ergometric stress test); take risk-adapted approach
Trials with 'clinically established IMPs' (e.g. bioequivalence trials for generic medicines applications)	• Range between 50 and 90 bpm is recommended • Potentially, heart/pulse rate <50 and ≥45 bpm acceptable in case of normal thyroid function (medical history, physical examination, TSH) and no signs of diseases associated with bradycardia (e.g. orthostasis and dizziness) •Some stakeholders consider heart/pulse rate <45 bpm acceptable in case of above stated criteria plus normal cardiological examination (including echocardiography and ergometric stress test); take risk-adapted approach

IMP investigational medicinal product, *TSH* thyroid-stimulating hormone

Eur J Clin Pharmacol 2017; 73: 409–16

Zdravi dobrovoljci

Table. 3 Laboratory parameters—normal ranges/clinically acceptable ranges

First-in-human trials	•Relevant hepatic parameter not to exceed ULN: ALT, AST, bilirubin (except in case of Gilbert's disease*) *In case of Gilbert's disease, elevated bilirubin not clinically relevant, yet may hamper interpretation of potential drug effects • Relevant renal parameters not to exceed ULN: creatinine, estimated GFR according to suitable formulae • Amylase and lipase to be interpreted in clinical context • Protocol to present rationale whether additional laboratory parameters required not to exceed reference ranges
Trials with 'clinically established IMPs' (e.g. bioequivalence trials for generic medicines applications)	• Slight elevation acceptable for hepatic parameters if no indication of apparent disease: 10% above ULN for ALT, 20% above ULN for AST or bilirubin (except in case of Gilbert's disease*) *In case of Gilbert's disease, see above • Slight elevation (10%) acceptable for renal parameters (except for creatinine**) if no indication of apparent disease **As creatinine especially in healthy male subjects also may reflect physical activity, protein intake by food, body height and muscle mass, some authors deem a slight elevation of creatinine up to 0.1 mg/dL above ULN as acceptable • Protocol to present rationale why these abnormal laboratory parameters seem acceptable

IMP investigational medicinal product, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *AP* alkaline phosphatase, *GGT* gamma-glutamyltransferase, *ULN* upper limit of normal, *GFR* glomerular filtration rate

Eur J Clin Pharmacol 2017; 73: 409–16

Zdravi dobrovoljci

Table 4 Stopping rules for first-in-human trials

Individual subject	•Coding adverse events and laboratory abnormalities according to e.g. CTCAE criteria/grades may facilitate definition of stopping rules, even though CTCAE not really suitable for healthy subjects
	• 1 adverse event of severe intensity (Grade 3*) *Some stakeholders apply this stopping rule only in case of a causal relationship with the IMP
	• 1 serious adverse event
	• Relevant signs or symptoms affecting subject safety
	• Decision always taken by the investigator
Dose group/cohort (stop of further dose escalation)	•≥50% of subjects of the preceding dose step experienced adverse events of moderate (Grade 2, safety alert, 'warning signal?') or severe (Grade 3) intensity considered to be drug-related (selective unblinding)
	• 1 serious adverse event suspected to be drug-related (unblinding advised) = 1 serious adverse drug reaction
	• In case trial to be continued following safety consultation between all stakeholders, substantial amendment required
Termination of entire trial	• Decision taken by mutual agreement between investigator and sponsor

IMP investigational medicinal product, *CTCAE* Common Terminology Criteria for grading of Adverse Events developed by the National Cancer Institute (1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = death), version current at the time of publication of this consensus paper: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Eur J Clin Pharmacol 2017; 73: 409–16

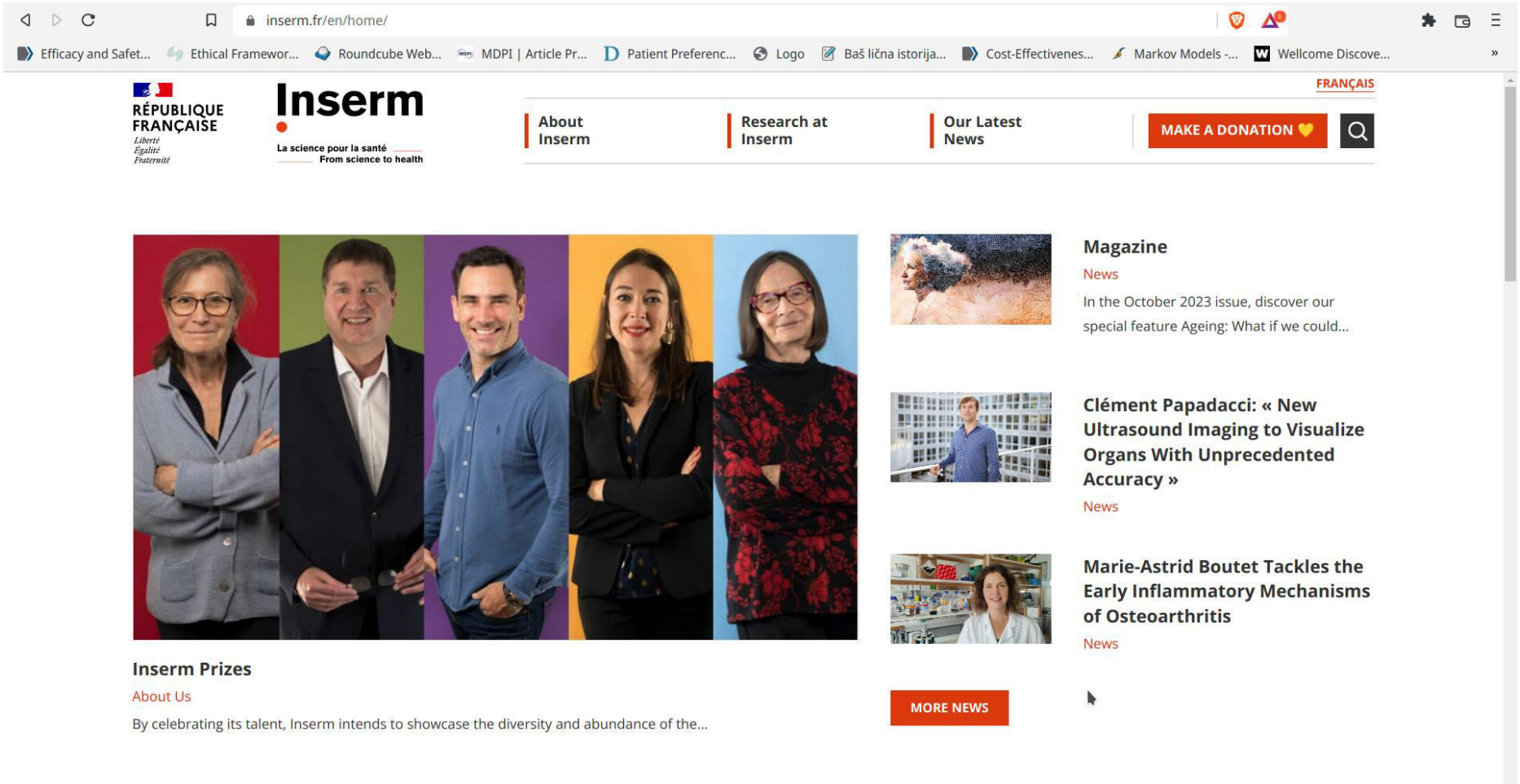
Zdravi dobrovoljci

Table 5 Stopping rules for other/later phase I trials

- General risk assessment based on
  - exposure (e. g. high exposure in drug-drug interaction trials, supra-therapeutic exposure in thorough QT trials)
  - frequency of relevant adverse events
- Protocol to define stopping rules and decision making process for individual subjects, cohorts, and entire trial

Eur J Clin Pharmacol 2017; 73: 409–16

L'Institut national de la santé et de la recherche médicale (Inserm)



https://www.inserm.fr/en/home/

VolREthics

- Ciljevi:
  - Stvaranje svesti o specifičnostima zdravih dobrovoljaca kao učesnika istraživanja
  - Promovisanje **Globalnog kodeksa** ponašanja za zaštitu prava, dobrobiti i bezbednosti zdravih dobrovoljaca
- Situacije u kojima su zdravi dobrovoljci izloženi najvećem riziku da budu:
  - iskorišćavani kroz ponovno učestvovanje ("komercijalna ispitivanja") i/ili
  - oštećeni (npr. FIH ili studije sa izazivanjem infekcije)

Eur J Clin Pharmacol 2017; 73: 409–16

VolREthics

- Radne grupe (WGs):

1 – zaštita od eksploatacije/promocija interesa i dobrobiti učesnika

2 – zaštita od oštećenja (harm)

3 – obezbeđivanje validnosti studije, principi 4R (*Respect, Reduce, Refine, Replace*)

Eur J Clin Pharmacol 2017; 73: 409–16

VolREthics

- WSG 2:

1 – fizičko oštećenje (subjektivno ili objektivno)

2 – druge vrste oštećenja/ugroženosti (etičko, psihološko, socijalno, ekonomsko, pravno i ugrožavanje familije ispitanika)

  - rizik od oštećenja:
    - ispitivanim medicinskim proizvodom
    - procedurom ispitivanja (uzimanje uzoraka krvi, bronhoskopije i dr.)
    - uslovima ispitivanja (izolovanost od članova porodice i dr.)

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Zaključak

- Studije I faze na zdravim dobrovoljcima će se uskoro sprovoditi u našoj zemlji (priznanje našem zdravstvenom sistemu!)
- Učestvujemo u donošenju novih dokumenata, odnosno međunarodnih standarda za takve studije
- Time se jača uloga kliničkih farmakologa (neophodno formiranje više Odeljenja kliničke farmakologije u našim kliničko-bolničkim centrima i dodatna edukacija)

Eur J Clin Pharmacol 2017; 73: 409–16