Vanemate ja kliinilised (ravim)uuringud

Tuuli Metsvaht

Doktorikooli seminar

juuni 2017, Tartu

Kirjanduse ja oma uurija kogemuse põhjal

- Vanemate arusaam olukorrast laste ravimkasutuses
- Kuidas ja mille alusel vanemad otsuseid teevad
- Informeeritud nõusolek
  - Mida pt esindajad arvavad
  - Lapse kaasamine nõusoleku protsessi
- Mida meie saame teha

Ravimid ja lapsed

Lastel kasutatavad ravimid

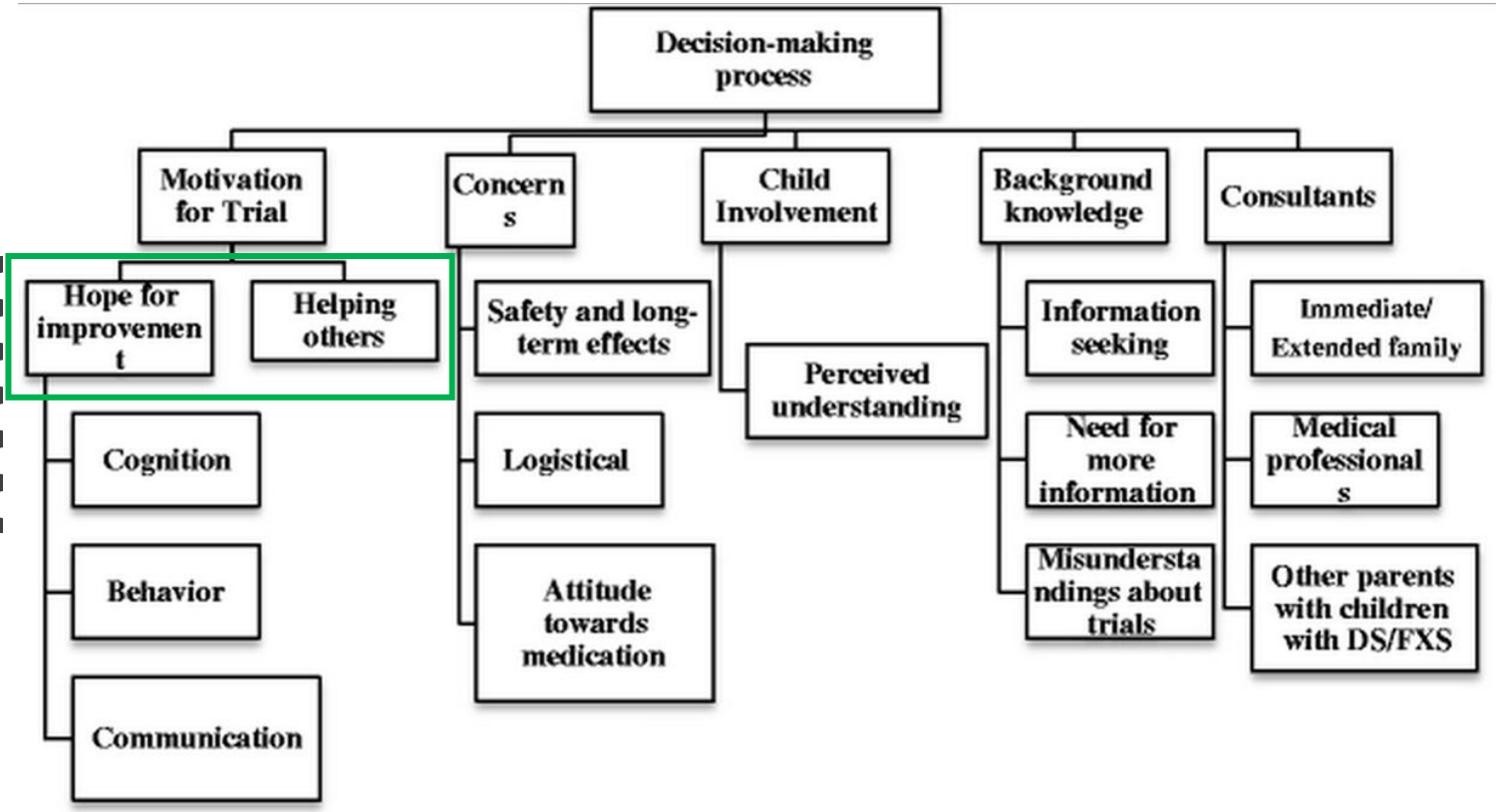
- 9-78,7% off-label
- 0.3-35% unlicensed

Vanemad

- 89,5% peab haiglas ja 80% perearsti poolt lapsele kirjutatud ravimeid ohutuks
- 30% on teadlikud off-label ravimite kasutusest lastel
- Kui off-label kasutust on selgitatud, peab ravimeid ohutuks 60% vanematest

Gore R[1], Chugh PK[1], Tripathi CD[1], Lhamo Y[1], Gautam S[1]. Curr Clin Pharmacol. 2017 Mar 17. doi: 10.2174/1574884712666170317161935;
Bang V et al. Int J Risk Saf Med. 2014;26(2):61-70. doi: 10.3233/JRS-140613

Otsus osaleda/mitte osaleda kliinilises uuringus



Reines, V., Charen, K., Rosser, T. et al. J Genet Counsel (2017). doi:10.1007/s10897-017-0111-x

Enamus vanemaid on positiivselt meelestatud …

- 24 lapsevanemat (22 ema, 2 isa) 15 DS, 9 FXS
- Suhtumine kliinilistesse uuringutesse:
  - 18 positiivsed (2 ei sooviks oma lapse osalemist uuringus!)
  - 3 negatiivsed, 3 neutraalsed

- “I think [clinical trials] are a miracle, it's an amazing time to live in and we’re honored to be a part of something, to be actually looking at fragile X itself and not just the symptoms.”
- “If we can do something that helps us and helps research out too, to help better somebody else's life and better his life too-I think it's a good thing because it could help everybody.”

Reines, V., Charen, K., Rosser, T. et al. J Genet Counsel (2017). doi:10.1007/s10897-017-0111-x

Kahtlejad

- “I have positive feelings about them just as I think we can learn from them.”
- “[drug trials] are necessary, I wouldn't volunteer my children for them. I would really have to know that there would be minimal [harm] to my son. I would be devastated if I did something that you know cause[d] more harm to him.”
- “I’m not sure because of all of his health problems. I’m so afraid to introduce anything right now.”
- “I guess it would be a drug by drug basis. I mean some of them you’re not going to know any side effects at all.”

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Negatiivsed

- “I’m kind of iffy about [trials], because my concern would be the long-term effect of the drug and my concern would also be if … there's any … side effects.”
- “as a parent I would not expose my child to a clinical drug trial.”

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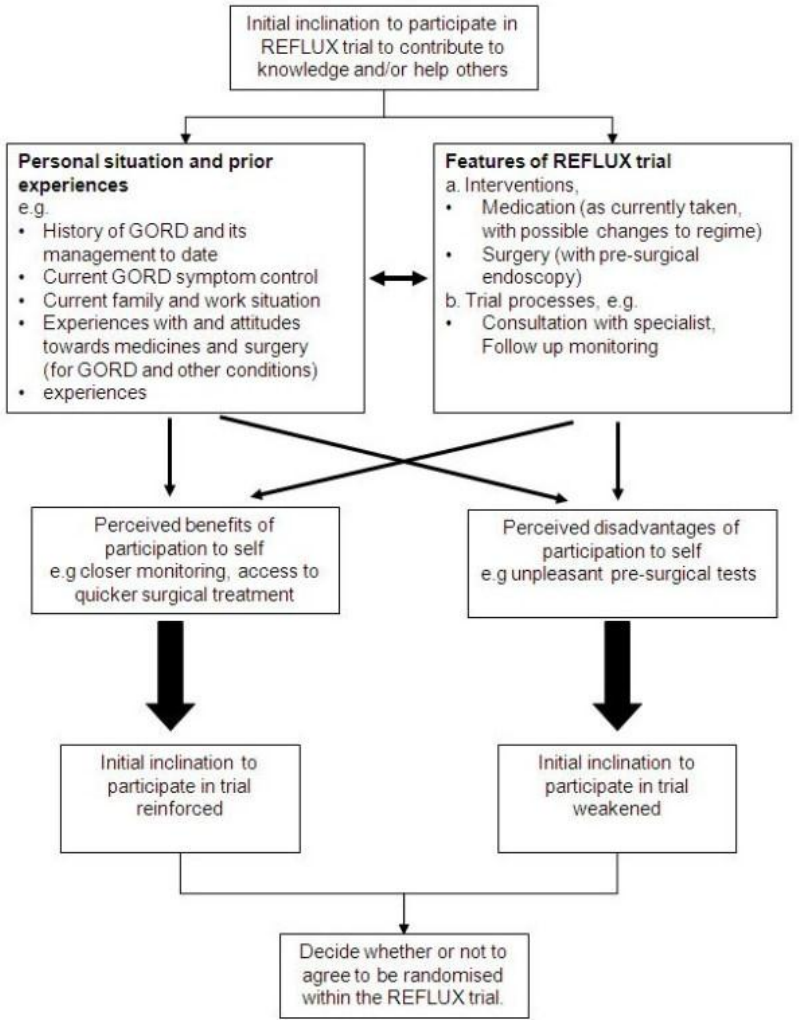
Tingimuslik altruism (conditional altruism)

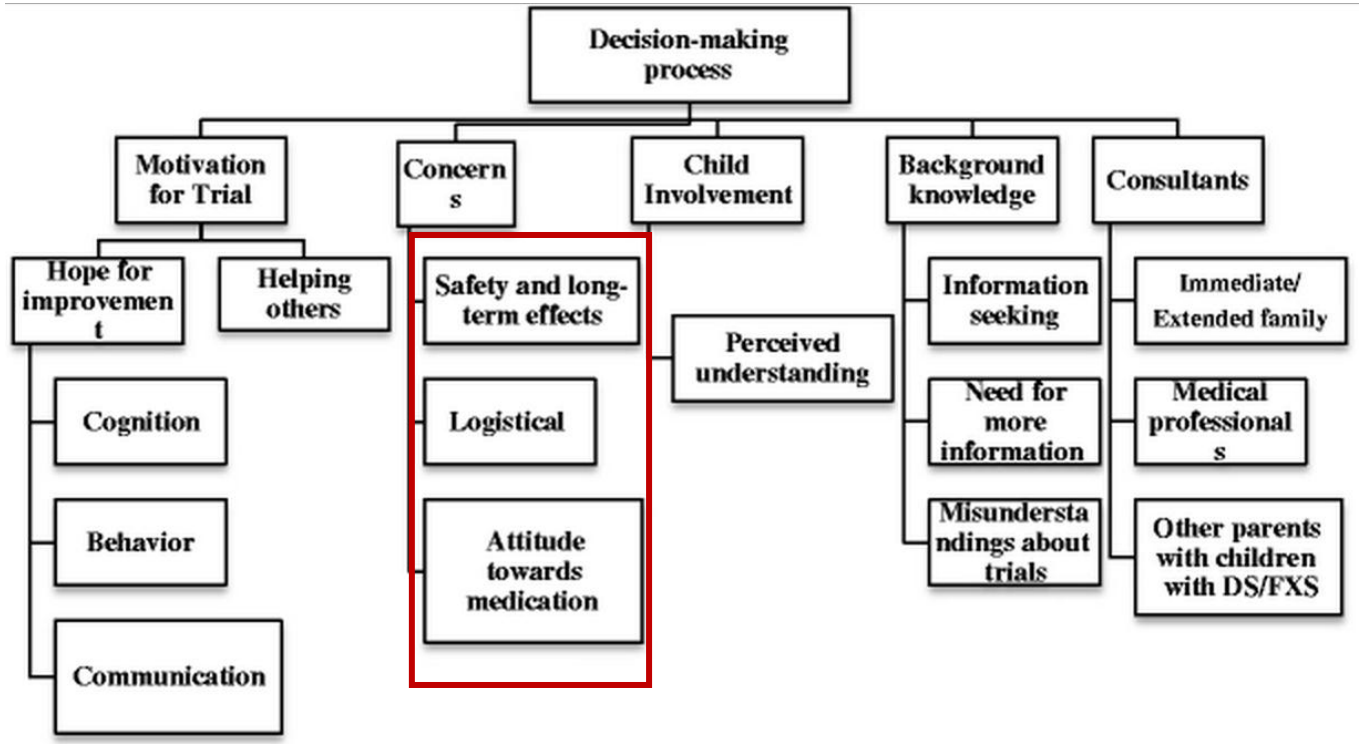
Soov aidata teisi kallutab inimest uuringutesse pooldavalt suhtuma, aga osalemine saab teoks, kui uuringust tõuseb inimesele kasu

- Spetsialisti konsultatsioon
- (kiirem) juurdepääs soovitud ravimeetodile (kirurgia vmt)
- Täpne jälgimine
- Kahju puudumine!
- Keeldujatel olemasoleva raviga hea vaevuste kontroll



SK McCann et al. Trials. 2010; 11: 31. online 2010 Mar 22.doi: 10.1186/1745-6215-11-31

Otsus osaleda/mitte osaleda kliinilises uuringus



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Vanemad vajavad informatsiooni

“I just don’t know enough about [clinical trials]…so I would really have to be educated that this was really the right thing.”

Paljud vanemad ei mõista uuringu eesmärke õigesti!

Nõus osalema,

- kui ravimil on juba FDA heakskiit
- Ei ole kõrvaltoimeid ega võimalikke pikaajalisi mõjusid …

Therapeutic misconception (Appelbaum 1982)

- "… when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial"
  - Potentsiaalselt eluohtlik/ eluiga lühendav haigus ja piiratud ravivõimalused – soodne võimalus mitte-asjakohaste ootuste tekkeks ja nende ära kasutamiseks
  - Põhjuseks emotsionaalne haaratus pigem kui uuringu eesmärkide mitte-mõistmine

GE Henderson et al. PLoS Med. 2007 Nov; 4(11): e324 HL Peay et al. Clin Trials. PMC 2015; 11:77-85

Therapeutic mis-estimation

- kasu/ riski suhte üle- või alahindamine kliinilises uuringus

- Enamus vanemaid suudab tegelikult vahet teha ootuse (“what I thought would happen”) ja lootuse vahel
- Emotsionaalne ootus sageli ebarealistlik
  - Uurija/klinitsisti roll?

Infoallikad

- Pereliikmed
- (Sama probleemiga laste) vanemate ühendused
- Laiendatud perekonna liikmed
- Raviminfo
  - Loomkatsed, olemasolev ohutuse info
- Sponsor
- Meditsiinipersonal

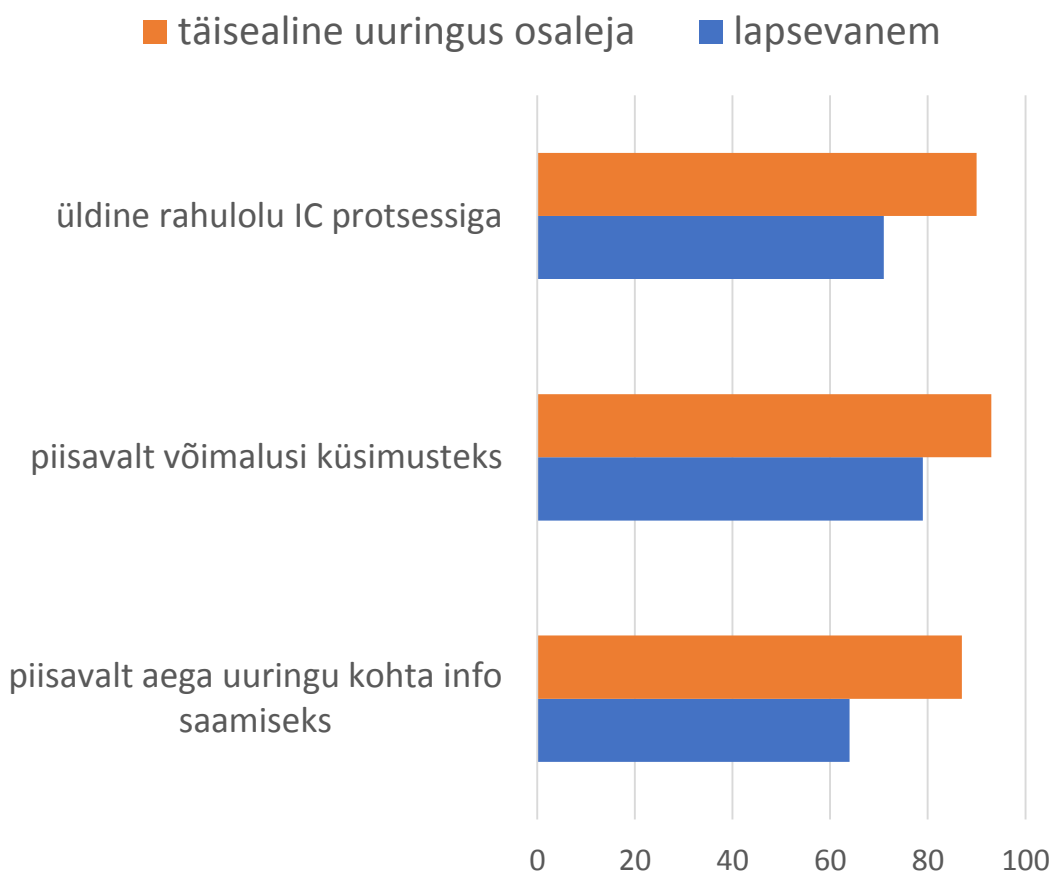
Reines, V., Charen, K., Rosser, T. et al. J Genet Counsel (2017). doi:10.1007/s10897-017-0111-x
HL Peay et al. Clin Trials. PMC 2015; 11:77-85

Informeeritud nõusolek: vanem on uuringus osalevast täiskasvanust pigem nõudlikum

- Keerulised uuringuprotokollid
- Emotsionaalne pinge
- Sõltuvus lapse arstist

- Soov lähtuda lapse parimatest huvidest ja hirm teha „vale“ otsust

- Vanemad vajavad aega, et otsustada!



HL Peay et al. Clin Trials. PMC 2015; 11:77-85; M Nabulsi et al. J Med Ethics. 2011 Jul;37(7):420-3
TH Truong et al. Pediatr Blood Cancer. 2011 Dec 1;57(6):998-1004

Informeeritud nõusolek

“Any positive gain, you have to do it for the other boys coming up, you know? So you just--you feel committed …you hope and pray that it could be with your boy, but if not, then future boys.”

Jah

- Tunne, et panustatakse, ollakse kaasatud
- Võimalus midagi ära teha (võimestamine)
  - Lootuse füsioloogiline toime
- Riski/ kasu suhe
- Otsese kasu ootus
- **Usaldus arsti/ raviasutuse vastu**
- Majanduslik kasu
- Varasem positiivne kogemus
- Altruism <50%

Ei

- Liiga keeruline informatsioon
  - Mõiste „randomiseerimine“
- Kõrvaltoimed
- Lisauuringud/ analüüsid
- Logistika

M Nabulsi et al. J Med Ethics. 2011 Jul;37(7):420-3; HL Peay et al. Clin Trials. PMC 2015; 11:77-85

CloSed

Clonidine for Sedation of Paediatric Patients in the Intensive Care Unit

FP7-HEALTH-2013-INNOVATION-1

Deliverable D8.3 "Report on 1st workshop with PAB"

Mitmekeskuseline topeltpime III faasi uuring: klonidiini vs midasolaami sedatsiooniks lasteintensiivravi osakonnas.

Patsientide esindajate nõuanded

Informeeritud nõusolek: mitte ainult mis, vaid kuidas

- The PAB advises psychological support for patients/parents in case of Deferred Consent.
- **When something is ethically difficult it is not a reason not to do it at all. You need to consider the risks and inform the participants.**
- For the acute patients, **Deferred Consent** is worth considering; but **only at PICU's where the use of Clonidine is already part of the standard medical treatment**.
- For the not-acute patients the standard Informed Consent procedure is essential of course.
- It is important that the clinical trial protocol is ready for the discussion about information sheets concerning the exact Informed Consent procedure.
- It is important to inform patients and parents about the standard treatment and in which way the trial-treatment differs.
- Explain in which way the trial-treatment has an effect on the wellbeing/health/comfort of the child.
- Explain to patients and parents **why the researchers chose Deferred Consent instead of Informed Consent**.
- Information to parents in a Deferred Consent situation: It's important to first explain the treatment the child is receiving right now (according to clinical trial protocol) and the main difference with standard clinical care. Next, tell the importance of this clinical trial (Clonidine is now being used off-label, that's not ethical) and next, explain why is chosen for a Deferred Consent procedure versus an Informed Consent procedure.

Informeeritud nõusolek: mitte ainult vaid kuidas

- Information and communication is important. **Verbal as well as non-verbal communication**.
- Physicians need to realize that **parents don't expect or anticipate the question: do you want to let your child participate in a clinical trial?** A parent's first instinct is to say no.
- Another important aspect is the vocabulary being used. For example **'medical trial' has a very negative connotation**. If possible, use other terms and when writing the Informed Consent material; consider every term that's being used.
- Explain from which point on you are going to gather data, before or after the signature. Especially in case of Deferred Consent.
- Make sure you **involve participating patients/parents long term**. Report preliminary results so they can respond on them (maybe they forgot to mention health issues/adverse events and do to the preliminary results they are triggered). Maybe a patient app is an option?
- The Informed Consent procedure and the clinical trial treatment have to be explained **face-to-face as well as in writing**.

Aeg on oluline …

Funded by the
European Union

4.3.2. Concerning time needed to decide

- Clinicians have to give patients and parents ideally 2 to 3 days. But at least more than 24 hours.
- Do not push patients or parents to make a decision.
- Give them telephone numbers where they can obtain more information.

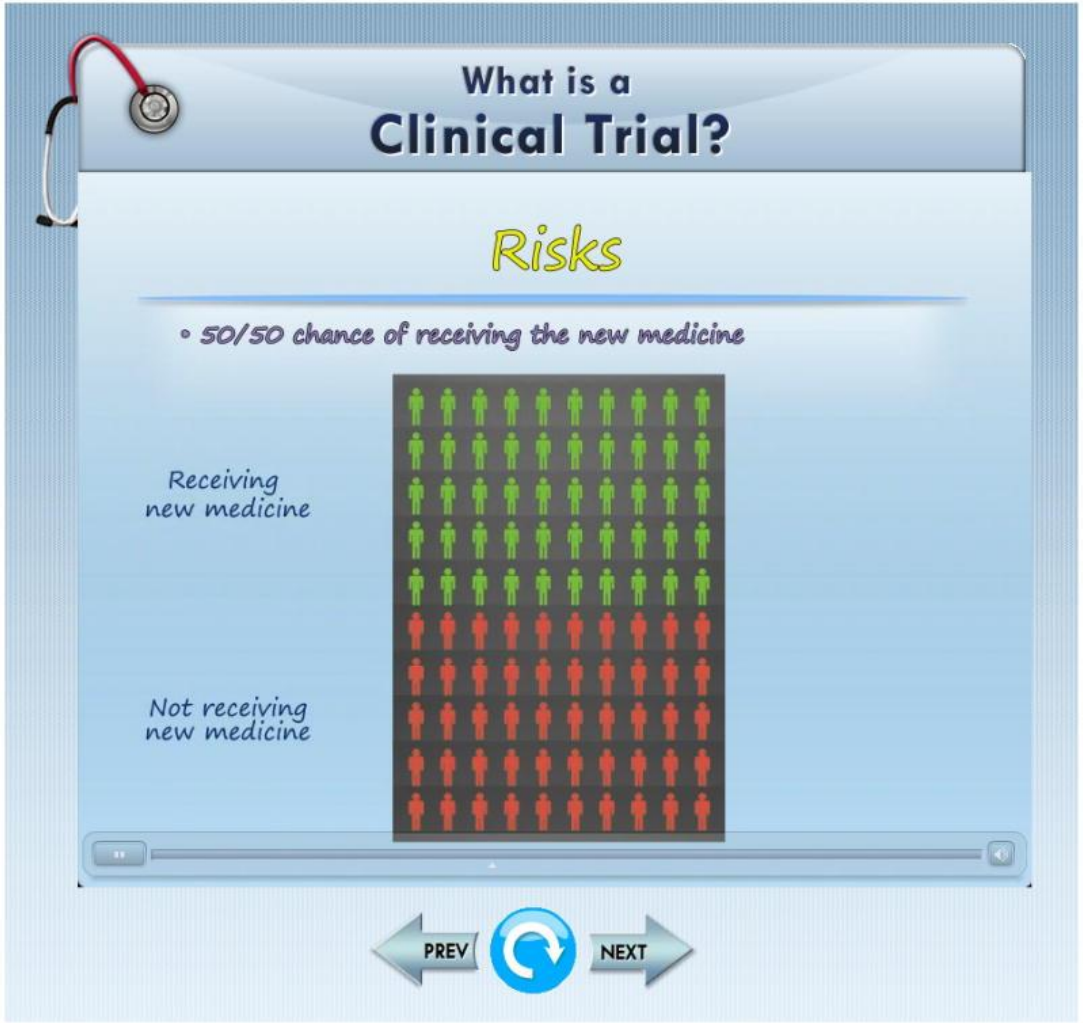
Pt arusaamise/ teadmise parandamiseks ei ole ühtset lahendust

Author (year)	Endpoint	Results
Agre and Rapkin (2003)	Knowledge	**No difference** among PICF, booklet, video and CAI programme, across patients from 18 trials
Brownet al. (2007)	Knowledge	**No difference** before and after physician participation in a communication skills training
Coyneet al. (2003)	Comprehension	**No difference** between easy-to-read consent statements vs PICFs
Hietanenet al. (2007)	Understanding	Better understanding of the main purpose of the trial among patients of physicians who received communication skills training (89% vs. 78%, P = 0.032). However, participants in both groups had misconceptions.
Hoffneret al. (2012)	Understanding	**No difference** between a video plus reading a PICF and PICF
Hutchisonet al. (2007)	Knowledge	Higher knowledge scores among participants who watched audio-visual information and read the PICF compared to PICF only (P = 0.0072)
Kasset al. (2009)	Understanding	Video group compared with NCI booklet only were 32 times more likely to believe that the purpose of an early phase trial was to examine safety, as opposed to efficacy of study drugs (OR = 32.31, P = 0.005). However, the video group tended to report that the reason they enrolled in an early phase trial was because their physician thought it would be a good idea (70.2% vs. 48.6%, P = 0.045) and patients might benefit from the drug (46.8% vs. 25.9%, P = 0.02).
Strevelet al. (2007)	Knowledge	Educational DVD group less likely to believe that the goal of phase I trials was to determine drug efficacy (P = 0.019), more likely to know phase I drugs have not been thoroughly studies in humans (P = 0.003) and less likely to believe that these new drugs have proven activity against human cancers (P = 0.008). No difference between the two groups on physician perception of patient understanding of phase I trials
Wrayet al. (2007)	Understanding	**No difference** in subjective QuIC scores were reported between participants who received only the NCI booklet and those who received the tailored brochure

PICF, Participant Information and Consent Form; QuIC, Quality of Informed Consent.

Või siiski?

- Interaktiivne informatsioon
  - Vanematel pole vahet
  - Laste arusaamine paraneb +2,8 (1,4-4,2) punkti võrra 0-18 p skaalal



Tait AR et al. Arch Dis Child. 2015 Jun;100(6):589-93

Saab suurendada pt rahulolu

Author (year)	Endpoint	Results
Brown*et al*. (2007)	Satisfaction with treatment decisions and the informed consent process	No difference in participant satisfaction of physicians communication skills training or not
Coyne*et al*. (2003)	Satisfaction with the ease of reading consent statements	Higher satisfaction with easy-to-read consent statements (*P* = 0.004) vs PICFs
Hietanen*et al*. (2007)	Satisfaction with the informed consent process	Higher satisfaction of patients of physicians receiving communication skills training (73%) vs control group (56%) (*P* = 0.003). The time given for decision-making was sufficient compared with the control group (98% vs. 90%,*P* = 0.004)
Hoffner*et al*. (2012)	Satisfaction with the DVD	Favourable experience in watching the Clinical Trial Video: 85% found the video an important source of information about clinical trials; 81% felt better prepared to discuss the trial with their physician; 89% helped family better understand clinical trials; and 73% helped the family to accept their decision about trial participation
Strevel*et al*. (2007)	Satisfaction with the DVD	Educational DVD group more likely to agree/strongly agree the video provided useful information (*P* < 0.001); the DVD as a good source of knowledge about phase I clinical trials (*P* < 0.031); they will have more questions to ask their physicians (*P* = 0.017) and; that a DVD helped them decide whether to enter a phase I clinical trial or not (*P* = 0.011)
Wray*et al*. (2007)	Satisfaction with decisions and reading materials	No difference between NCI booklet or a tailored brochure. High levels of satisfaction with decision-making and with materials reported for both

Kao C.Y., Aranda S., Krishnasamy M. & Hamilton B. (2017) European Journal of Cancer Care 26, e12424, doi: 10.1111/ecc.12424

Lapse kaasamine uuringus osalemise otsusesse: kognitiivne fn, mõistmisvõime, vanus

- “[w]e discuss so many things with him that we would, you know, discuss all of this with him. He’s really fortunate to be able to comprehend a great deal.”
- “I'm sorry, he doesn't have the mental capacity to decide.”
- “I would probably need to make [the decision for him to take a lifelong drug] when he is old enough to make the decision too, I guess.”

Reines, V., Charen, K., Rosser, T. et al. J Genet Counsel (2017). doi:10.1007/s10897-017-0111-x

“I think because of the cognitive delay, kids with DS are going to be very easily swayed by people who may or may not have their best interest at heart … so I’d be very careful about how I involved him. I would want his opinion, but I would also want him to really understand the decision.”

Hirm lapse ärakasutamise ees!

Reines, V., Charen, K., Rosser, T. et al. J Genet Counsel (2017). doi:10.1007/s10897-017-0111-x

Family/children friendly research

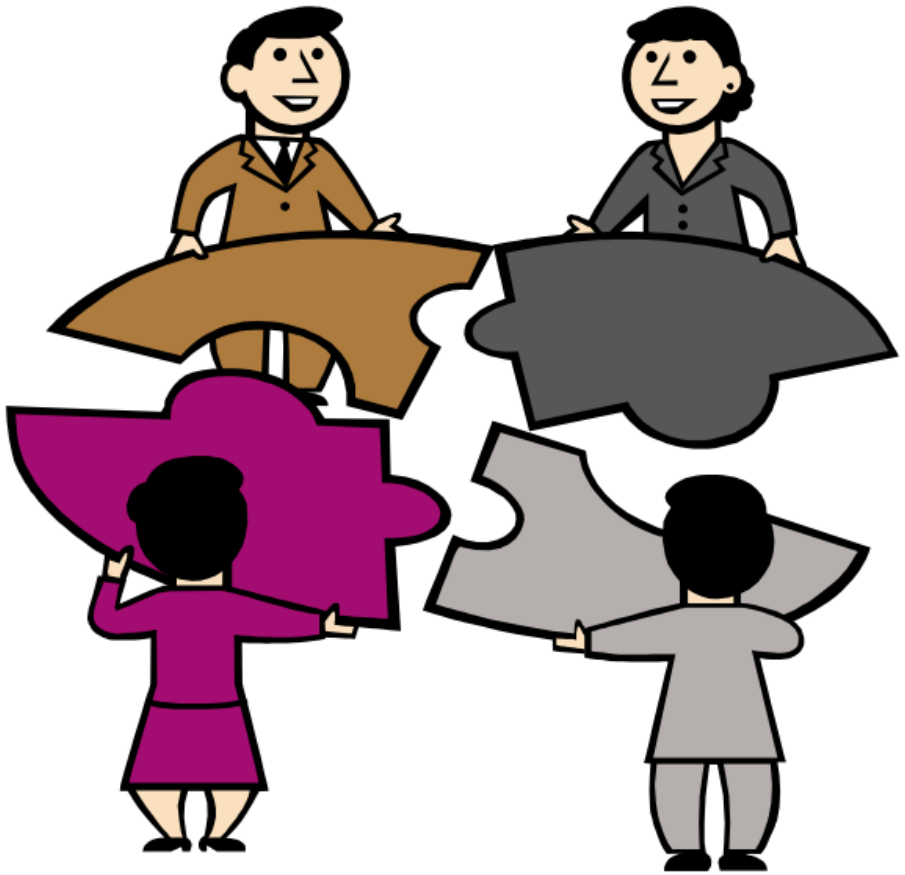
- Reseach with children and parents needs more time and special communication training („research language“ – „how research works?“)
- Just a research object, like an animal
- Worried about risk of bad outcomes or risk on the consequences, e.g. drug studies
- Parent and parent organisations feel often not accepted and respected
- Information should be available in different languages e.g. for immigrants

Aitäh, S. Mader, European Foundation for the care of newborn infants

Different understanding in „working together“

Healthcare Professionals

Industry



Parents

Third parties
Policy makers

Aitäh, S. Mader, European Foundation for the care of newborn infants

Kokkuvõtteks

Vanemate suhtumist kliinilisse uuringusse mõjutab

- Usaldus arsti/ raviasutuse vastu
- Võime mõista esitatavat informatsiooni ja vajadusel küsida/otsida lisa
- Kaasatus

- Vanemate osalus kliinilistes uuringutes on oluline
- Kuidas ühtlustada arusaamad koostööst?