Informed consent: challenges in complex and novel trials, information of trial subjects

ACT EU Annual Meeting

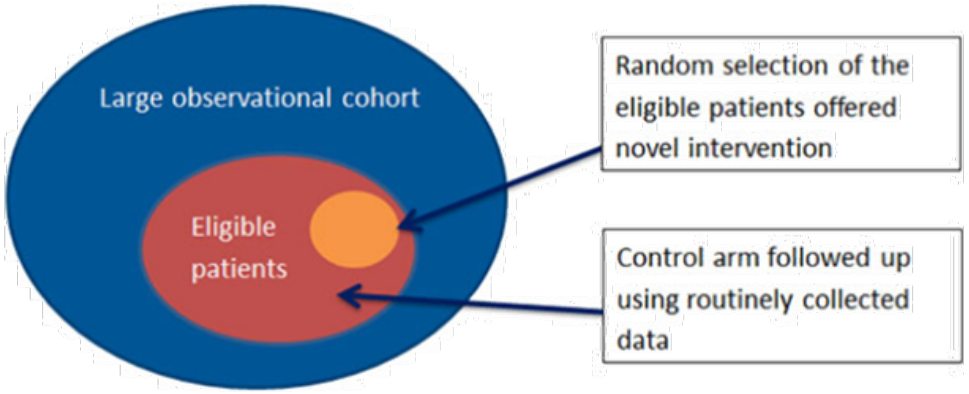
29 October 2025

Session 4

Registries will increasingly be used for (May 2023)

The cmRCT study design is a type of pragmatic trial. It is also known as a 'trial within cohort' study design (TwiCs).

Figure. Cohort multiple randomised controlled trial



Cluster cmRCTs are a variation on this design using groups (clusters) of patients rather than individuals randomised to different treatments (similar to cluster RCTs). For example, a cluster might be within a GP practice, hospital or community. This can increase the speed of recruitment to the trial and help reduce costs because interventions are administered in fewer places.

IMI GetReal http://www.imi-getreal.eu

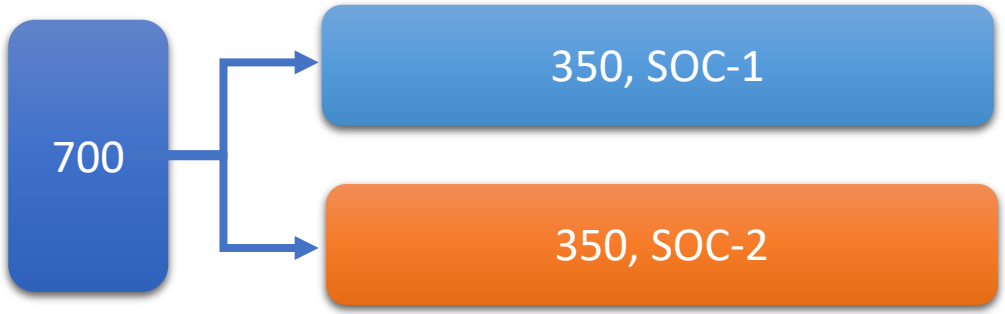
Cohort multiple randomised controlled trial (cmRCT)

(Clinical Trials Transformative Initiative)
https://www.ctti-clinicaltrials.org/projects/registry-trials

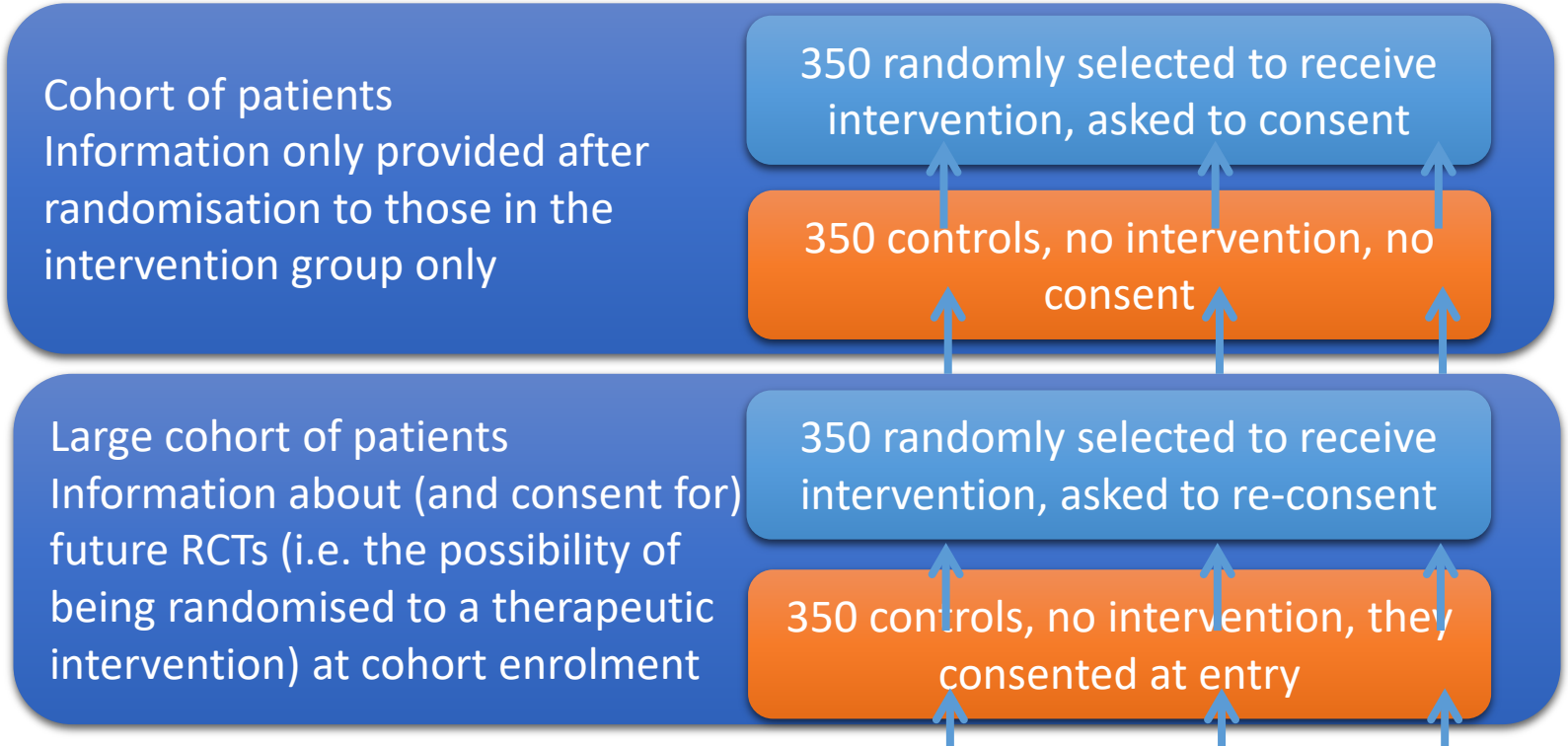
Credits: Peter Mol, kick-off meeting, More-Europa Project

Treatment strategy trials, Pragmatic trials, TwiCs. Is consent always needed? for all?

Pragmatic trial, comparison of 2 SOC treatments (authorised)



Patients would receive SOC-1 or SOC-2 anyway
Instead of flipping a coin yourself, treatment assigned by a random process. Consent, or no consent?



Zelen method

Trial within Cohort with broad consent at entry, for all

Those unselected for the intervention: not actually allocated to 'treatment as usual'

Ethical aspects

- Is it ethical not to inform potential trial subjects about interventions that they are not then subsequently offered if they are in the control group (treatment as usual)?
- Young-Afat *et al*. **Oncology patients were found to understand and accept the Trials within Cohorts design.** J Clin Epidemiol. 2021 Feb

After all

- Analogy with lottery winners who are 'selected', where there is no sense in which ticket holders who don't win are 'allocated' to a losers' group
- Single-arm trial and external controls (from the placebo arm of a previous trial, or from patient registry): are controls informed? Asked to consent for secondary use?

Public debate

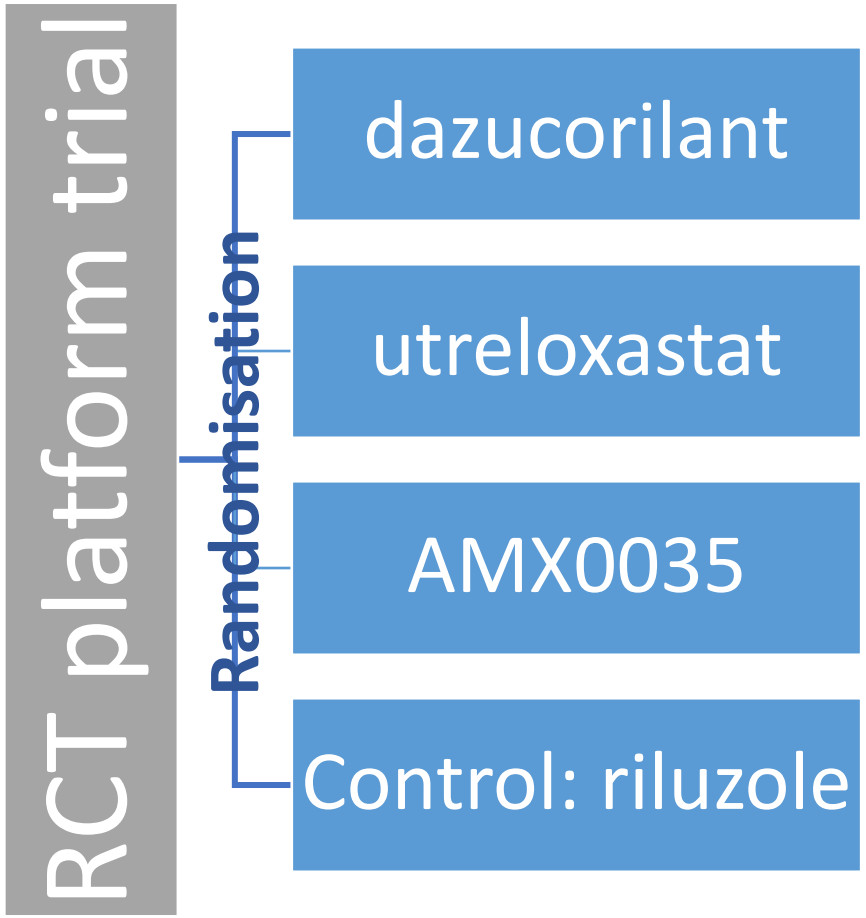
- Wellcome Trust / Uni. Sheffield 2016
- Relton, C., Burbach, M., Collett, C. *et al.* **The ethics of 'Trials within Cohorts' (TwiCs)**: 2nd international symposium. *Trials* **18** (Sup 2) (2017)
- 20 studies reviewed and commented
- For ACT EU MSP AG?

In which situations? Context of use

Control arm / placebo hardly acceptable by participants	• Short-life expectancy: eg AZT trials for HIV/AIDS, ALS trials • Prior knowledge on product (immune therapy in oncology, CART-T cells…). TwiCs or SAT with external controls?
Psychedelic products	• Eg resistant depression: participants in control arm don't experience the psychedelic effect. High risk of dropping out • EMA workshop report here
Emergency medicine research	• Where consent is not possible
And many others	• …

Platform trial, smarter trials
Amyotrophic Lateral Sclerosis (ALS)

- R&D



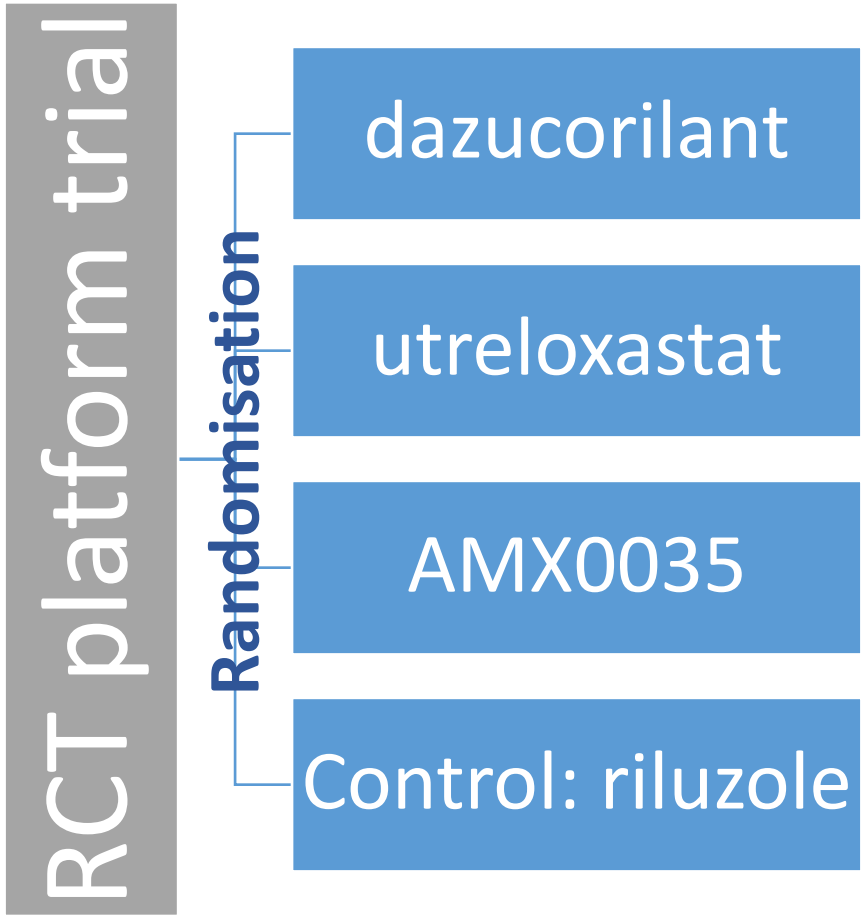
- Risk to be randomised to control arm: 25%. Even more *resentful demoralisation* for those assigned to control arm?
- Cannot be easily blinded: 3 placebo needed in each arm, or each product exact same presentation

Platform trials / Multi-factorial trial design: other questions

1. When an arm becomes futile, can patients be randomised to other arms?
    1. Ethical not to re-randomise them to other arms, as trial continues?
    2. Internal validity if participants switch from one arm to another one?
    3. A wash-out period needed? How long?
2. Switch-over based on interim results?
    1. If one arm has positive results?
    2. Should all other arms be continued? What if loosing a chance? Re-consenting?
3. If one of the trial products is authorised, to stop or to adapt?
4. Patients not in trial: possibilities for a platform compassionate use?

ALS: smarter trial, smarter compassionate use?

- R&D



- For patients not included in CTs

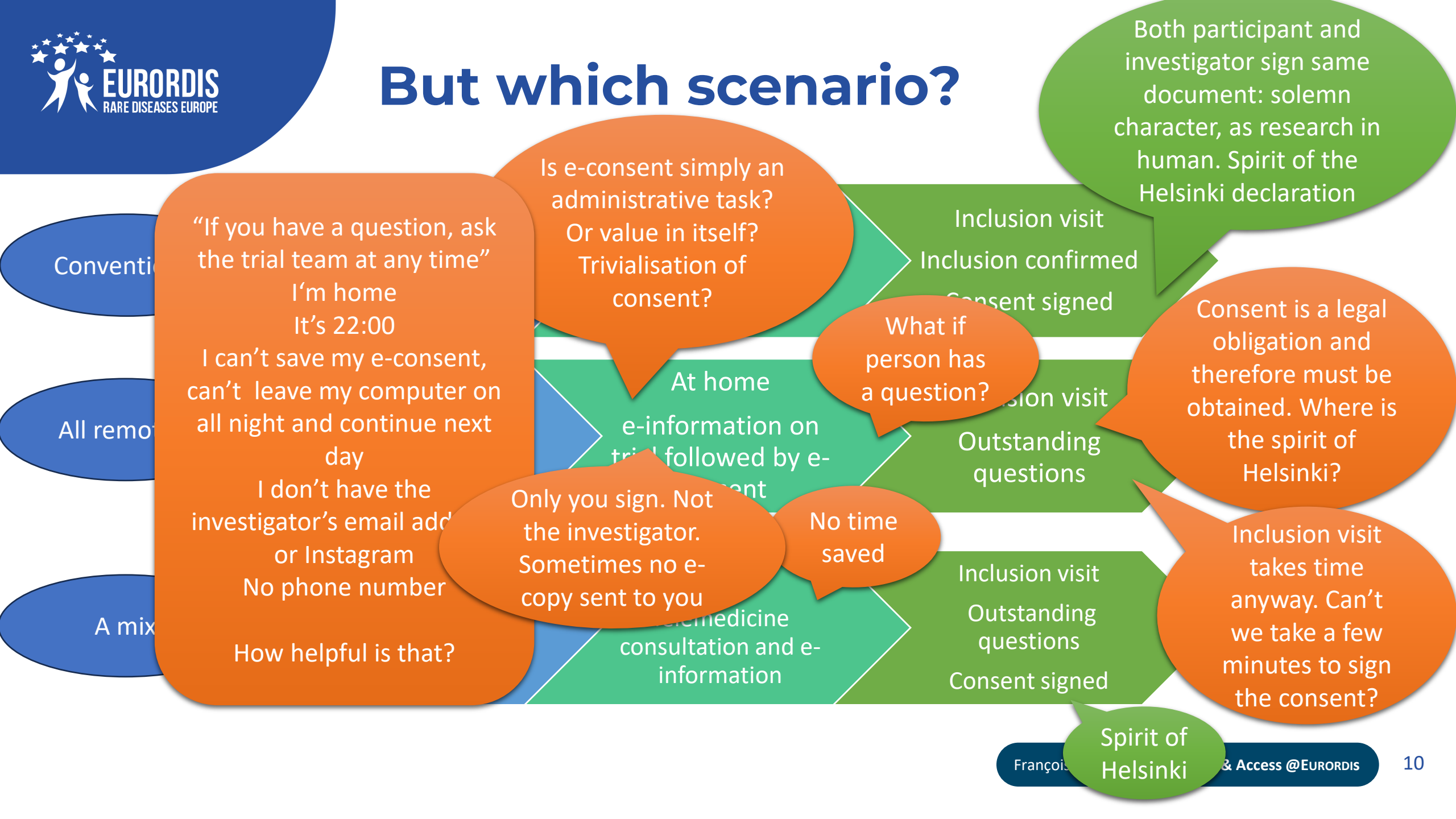
E-consent / e-assent: Informing, and obtaining consent

- Discussions focused mostly on
  - The official electronic signature versus a simpler signature
  - The need to confirm with a clinical investigator

- E-consent: for investigators to gain time?
  - Repeating the same thing to 25 potential participants = 25 x 20 minutes or more (500 min)
- Or to improve the process, and the quality of the consent? videos, animated graphs…

- E-consent / e-assent
- At site visit with investigator: can focus on aspects important to the potential participant

But which scenario?



Maybe a better practice is

As experienced back in 1983

Before first national legislation on clinical trials

Such collective approaches were banned, to “protect us” (medical secrecy)

1. Trial team invites 25 potential participants in a meeting
2. Investigator explains the trial (30 min.)
3. Participants ask questions (60 min.)
4. New-comers benefit from the experience of other patients, and can discuss with each other
5. Total time = 90 minutes
6. Time saved = 410 minutes
7. And participants are better informed

Genetic information in clinical trials

Repo4EU project on drug repurposing
Annual Conference 24-26 September 2025

Analysis of CTIS using Large Language Model: high prevalence of trials with Whole-Genome Sequencing

- Poor differentiation between selection procedures, mandatory trial procedures and future research
- Inconsistent policies on managing and disclosing incidental findings
- Insufficient information to ensure participant understanding
- Country-specific differences in the structure and detail of consent forms

Ana Sofia Carvalho, School of Medicine and Biomedical Sciences, Uni. Porto

AI agents can help! Chatbots, natural language etc. Research proposals

Trial result lay summaries

- A template, an army of writers for lay summary results. They decide which information is important to you?
- Or an AI agent specifically trained, able to detail aspects that are important to you?

Clinical Trial Register / Trial map

- Chatbot can help navigate the database, compare my health medical records with inclusion/exclusion criteria

Trial design

- Randomised or single arm trial with external controls? See workshop 3 November

Complex trials

- How to explain the trial design? How clear is the information?

Bayesian approaches

- Complex for clinicians and regulators, how to explain them to patients?

Consent and information

- An AI agent to explain the protocol
- An AI agent to obtain consent
- Better performance than a clinician?
- Not limited to 20 minutes
- Can adapt to different health literacy levels

Consent withdrawal: treatment or trial?

- The importance of securing data already collected, and to make all necessary efforts to continue collecting data, without putting pressure on trial participant
- Or extract data from EHR and inform the trial own system?

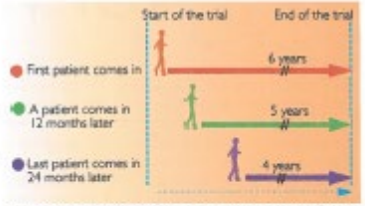
Recruitment & Retention - useful initiatives

Your follow-up

Why must SILCAAT last several years?

The aim of SILCAAT is to determine if IL-2 provides a long-term benefit for people infected by HIV. This is why your participation is needed for this length of time.

When you entered the SILCAAT trial, your doctor informed you that your participation was planned to last for a minimum of four years. This is, in effect, the time required if you entered SILCAAT recently. However, as the trial will only be complete when all participants have at least four years of follow-up (see the diagram), those of you who first enrolled will be involved for up to 6 years. This may seem like a long time. If you have participated in other clinical trials before SILCAAT, you probably know that studies of anti-HIV treatments are usually shorter – generally 1 or 2 years. Why, then, is SILCAAT so lengthy?



As not all the participants enter the trial at the same time, the first ones come in will have a longer follow-up than the last ones.

What is known and not known

The answer to this question lies in our current knowledge on interleukin 2 (IL-2), the product being tested in SILCAAT, and in way HIV infection evolves.

Several trials have been conducted on IL-2 in recent years. Overall, they showed that IL-2 can stimulate the production of CD4 lymphocytes – the main HIV target cells. When a person takes IL-2 in addition to anti-HIV drugs (antiretroviral drugs), there is generally a significant rise in the number of CD4 lymphocytes. Moreover, this rise in the CD4 cell count from antiretroviral drugs combined with IL-2 is generally larger than that obtained with antiretroviral drugs alone. See page 4 of this issue of Liaison for the results of two recent trials that demonstrate this clearly.

Furthermore, studies have shown that the new CD4 lymphocytes obtained with IL-2 are fully functional, meaning that they may play their role to their full capacity against microbes that you may encounter (viruses other than HIV, bacteria, fungi, etc.). They may therefore play their part in organizing your immune defenses to fight these germs.

However, a crucial question remains to be answered: are the CD4 lymphocytes produced during IL-2 therapy truly beneficial to the patient? Many specialists believe they are, on the basis of available information. But believing is not enough: we need proof. Some might think that current anti-HIV treatments – multidrugs antiretroviral therapy (HAART) – are adequate. It is undeniable that they increase the CD4 lymphocyte count in a large proportion of HIV-infected individuals (even if it seems the combination with IL-2 leads to a higher and more rapid increase than on HAART only). We need to demonstrate and prove if IL-2 provides an extra benefit.

This is the focus of the SILCAAT trial: comparing the long-term outcome of HIV infection in two groups of seropositive people, one receiving antiretroviral drugs alone, and one receiving antiretroviral drugs combined with IL-2. This comparison will allow us to see whether the infection progresses less rapidly, or at the same rate, when a person takes IL-2. If the rate of progression is slower in people taking IL-2, it will mean that IL-2 is beneficial. If the rate of progression is equivalent, it will mean that IL-2 has no extra benefit.

Comparing health progressions over time

The only way to compare the progression of HIV infection in two distinct treatment groups is to analyse and compare the frequency of HIV-associated health problems, such as PCP and toxoplasmosis in each group. The occurrence of one of these health problems is a sign that HIV infection is progressing. If they are less frequent in the group receiving the additional IL-2 than in the group receiving antiretroviral drugs alone, it will mean that IL-2 offers a clear benefit.

Fortunately, HIV infection does not progress very rapidly. The average interval between the initial infection and the moment when the first symptoms occur is about 10 years. This means that SILCAAT participants will have to be monitored for several years to detect any difference in the rate of progression between the two treatment groups.

The first priority: treating you effectively

Because SILCAAT is a lengthy study, you may be tempted, sooner or later, to quit. Because you may find one day that you have "had enough", or perhaps you will hear about the arrival of very effective new drugs. Of course you are free to decide to withdraw your participation at any time. But before doing so, the most important question you should ask yourself is "Do I really need to change my treatment?" If the treatment you are taking in SILCAAT is effective, and if you tolerate it well, why change? Even if major progress has been made in the treatment of HIV infection in recent years, there are not really that many options. It may therefore be best to keep the other drugs for when they are truly necessary.

If the treatment you are receiving in SILCAAT is no longer very effective, your doctor, with your agreement, can decide to change it at any time, whether you are taking antiretroviral drugs alone or in combination with IL-2. Whatever the case, rest assured: your good health is your doctor's main preoccupation.

Your treatment

IL-2 "à la carte"

If you have been participating in SILCAAT for more than a year and are among those taking IL-2, your injection schedule will now have been tailored to your personal needs.

After a year of SILCAAT participation, you should have completed six IL-2 injection periods. If everything has gone as planned, your CD4 lymphocyte count has increased. The goal is now to maintain this for as long possible. Depending on how your CD4 lymphocyte count evolves, your doctor can offer you one of two options:

1 **If the rise in your CD4 count is only moderate,** it is possible to continue injecting IL-2 with the same frequency as initially, a 5-day injection period eight weeks later, for 1 additional cycle. After the 9th cycle, the injections will be spanned out, every four months, and this new frequency will be maintained until the rise in the CD4 cell count is judged satisfactory.

2 **If the rise in your CD4 cell count is sufficient,** regular IL-2 injection periods are no longer necessary. Your doctor will continue to monitor you, by a consultation every 4 months, and will only suggest a new series of IL-2 injections when necessary.

If your CD4 cell count remains stable over the following months or years, you will no longer need to have IL-2 injections. If, on the other hand, your count starts to decline, you will be offered a new IL-2 treatment period, or a series of treatment periods. But the decision to do so will be taken by your doctor on the basis of very specific criteria. This is because the CD4 lymphocyte count can fluctuate considerably from one month to the next, without a corresponding change in health. A head cold, a period of stress, a change in diet, and even intense physical activity can make the cell count fluctuate, independently of HIV infection. Thus, only a large, persistent decline will be considered significant. A simple reduction from 500 to 450 or 400 CD4/mm³ from one month to the next is nothing to worry about – a decrease of at least 25% is required to warrant a new IL-2 treatment period.

Don't forget the DAILY NOTEBOOK whatever your treatment is!

At each planned visit in the SILCAAT study your doctor will give you a daily notebook. This notebook is very important, both for you and your doctor and for the study. It allows you to note, on a daily basis, everything pertaining to your treatment or your health. If you are taking IL-2, you should also note each time of injection.

Preserve your health

This may seem tiresome, but this notebook helps your doctor give you the best possible treatment. For example, if you develop any pain, a skin rash, or diarrhea, note it in the diary, even if it seems just temporary. Your doctor will keep track of your notes at each visit, and will be able to take any necessary measures to preserve your health.

Sometimes a seemingly harmless symptom can indicate that a problem is developing. The faster it is treated, the better for you and your health. Also, by keeping up to date with your notebook, you will be sure not to forget anything during your next visit.

The other drugs also

It is also important to write down in your diary any other drugs and/or herbal therapy you take – as harmless as they may seem – be it for a mild infection (a cold or sore throat) or anything to help you sleep, for example.

This is important, because some treatments can interact with each other if they are taken around the same time, and can then lead to certain side effects. It is important for your doctor to know precisely what drugs you have taken in addition to your anti-HIV treatment. Once again, this will enable him or her to make any necessary steps.

Above all, the daily notebook is there to help you !

Your treatment

Interesting results

SILCAAT is not the only trial currently evaluating interleukin-2. During the scientific conference on retroviruses in Chicago last February, several important results were presented.

These results were obtained through medical research, meaning that they have to be interpreted carefully (several studies yielding similar conclusions must be done before something can be accepted as scientific fact).

The first trial was done in France by the National AIDS Research Agency (ANRS). The chief investigator was Professor Yves Lévy, who is also the chief investigator for the SILCAAT study. It compared antiretroviral drug therapy alone with antiretroviral drug therapy combined with IL-2. This trial (ANRS 079) differs from SILCAAT in that, at enrollment, participants had between 200 and 550 CD4 lymphocytes/mm³ whereas SILCAAT participants have less than 350/mm³ at enrollment.

Furthermore, ANRS 079 only involved 118 participants – far fewer than SILCAAT. In contrast, the dose of IL-2 was very similar to that used in SILCAAT (5 million units twice a day for five days, compared with 4.5 million units twice a day for 5 days in SILCAAT).

THE EDITORIAL BOARD

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For the SILCAAT trial, the Liaison editorial board is composed of the following persons: Pr Yves Lévy (trial principal investigator), Dr Anne-Marie Dubège (Chiron Laboratories), Dr Marchin Kwiatkowski (Chiron b.v.) and Franck Fontenay, François Houyez and Alain-Valny-Anne (RCP Communication).

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A good rise in the CD4 cell count

Data on the 80 participants with 74 weeks of follow-up in this trial were analyzed. Nearly 9 out of every 10 participants (89%) who received IL-2 had an 80% rise in their CD4 lymphocyte count (for example, an increase from 337 to 606/mm³), compared to nearly one in two (44%) of the participants who received antiretroviral drugs alone (a three-drug regimen combining Zerit®, Videx® and Crixivan®). Furthermore, the functionnality of the CD4 improves better in the group who received IL-2.

The proportion of patients with undetectable viral load was similar in both groups. Thus, the rise in the CD4 lymphocyte count was higher when antiretroviral drugs were combined with IL-2 than when they were taken alone, although there was no significant advantage in terms of viral load after 74 weeks of treatment. This is why the SILCAAT trial is so important. With its larger number of participants and a longer follow-up period, SILCAAT may detect what ANRS 079 could not : a possible action of IL-2 on viral load and/or opportunistic conditions.

If you are participating in SILCAAT and are not receiving IL-2, these results also have important implications for you. Treatment with antiretroviral drugs alone (without IL-2) also led to a large rise in the CD4 lymphocyte count, from an average of 337 to 577/mm³, i.e. a substantial benefit of +240 lymphocytes/mm³. Some participants had an even larger increase (up to +588 CD4/mm³), and the minimum was +237 CD4/mm³. Even if this was less than with IL-2, the rise in CD4 lymphocyte counts observed with antiretroviral drugs alone is significant. This means that you are not penalized by participating in SILCAAT, even if you are not taking IL-2.

Comparable results

The results of another interesting trial (ACTG 328) were also reported at the Chicago conference. This one was conducted in the United States. ACTG 328 involved 204 previously untreated participants with CD4 cell counts between 50 and 350 at trial entry – characteristics very similar to those of SILCAAT participants.

After twelve weeks of treatment with a three-drug regimen, participants with a viral load below 5000 copies/ml were divided into three groups: the first continued to take the same three-drug regimen; the second also started to inject IL-2 subcutaneously (as in SILCAAT); and the third started to inject IL-2 intravenously.

The results are in line with those of previous studies: after 84 weeks of follow-up, the CD4 lymphocyte count increased by at least 50% in 41% of the participants taking antiretroviral drugs alone, and by respectively 77% and 86% in the two groups also receiving IL-2.

Thank you!

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