EULAST Newsletter # 5

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Introduction

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15 patients included in EULAST - intervention
5 patients included within EULAST - NFU

Hello from Munich. All participating centers are now actively recruiting for the EULAST study across Europe. Especially in these challenging times, we must emphasize the importance of pan-European research and collaborations, and thus, lead this important trial to great success.

Despite being behind the recruitment goal, the EULAST group has now recruited more than 300 patients and some of the participating sites have successfully achieved their recruitment goals and will carry on including patients. This shows us how active this remarkable research group is and we should not forget that actively recruiting schizophrenia patients for a clinical trial is extensive, but very important, work. General predictors for a successful recruitment are that the design is clear, that the protocol is feasible (e.g. inclusion and exclusion criteria), that clear worksheets are available and that the coordinating team helps with words and deeds. All these factors are fulfilled for the EULAST trial and all PIs are grateful for the ongoing support by the EULAST core team. More specific predictors relate to the recruiting sites. At our and other participating site, a successful recruitment is achieved by having enough research staff involved in the trial, by providing a local clinical trial facility and most importantly by maintaining a close relationship between the research and the clinical teams. Especially in hospitals, the clinical routine care of schizophrenia patients takes a lot of time and these hospital doctors have usually neither the time to discuss a potential study inclusions nor the overview of respective study procedures. Therefore, clinical doctors should have at least one day per week to actively recruit for large-scale studies like EULAST or the core study team must be in a constant dialogue with the clinical team. Moreover, recruitment for clinical trials must be supported by experienced clinicians and consultants. One major issue is that junior doctors are assigned the responsibility to recruit for a clinical trial and in my view this is one of the most important bottlenecks.

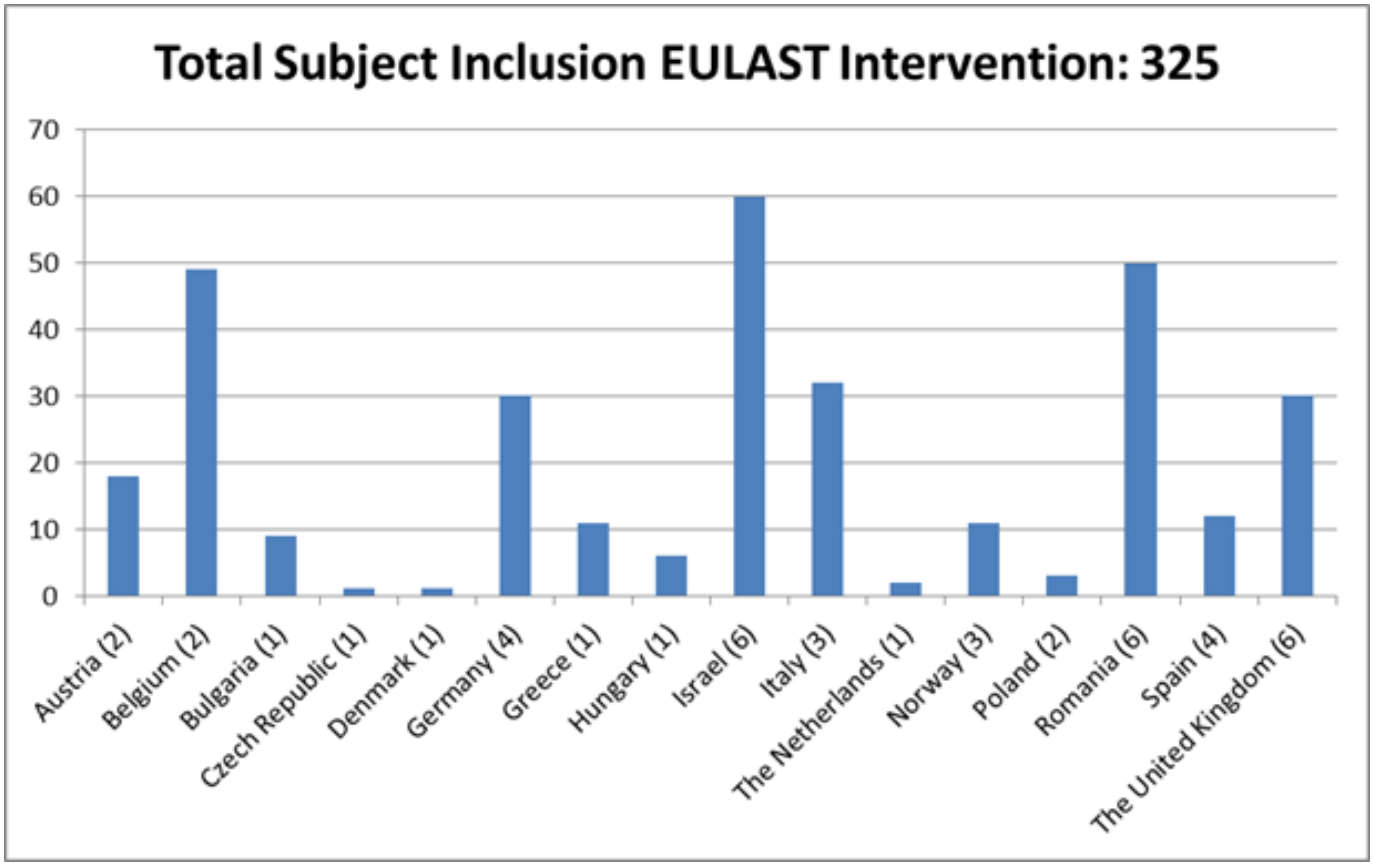
Clinical research is from the highest importance in all fields of medicine. However, in a patient population like schizophrenia, that is characterized by a poor long-term outcome and high disease-associated burden, and where novel drug developments are rare, head-to-head research regarding different treatment strategies is urgently needed and has the potential to improve our every-day care. The pretty ‘naturalistic setting’ and the specific design of EULAST will allow us to answer the question whether long-acting injections are

superior to oral treatment and whether more attention should be given to promote their use in early schizophrenia. It is an honor to be part of this European trial and we are awaiting with the greatest interest the outcome of the trial. However, before we all can see the results, all EULAST sites should give themselves a push to try to regain lost time. In the end, all of our work will benefit our patients' health.

Alkomiet Hasan
Principal Investigator – LMU Munich

Recruitment status

Twenty-two months have passed since the start of the EULAST trial Until now, 325 patients were included within 16 countries and 40 sites. This is an excellent achievement and therefore we would like to thank you all for your work!

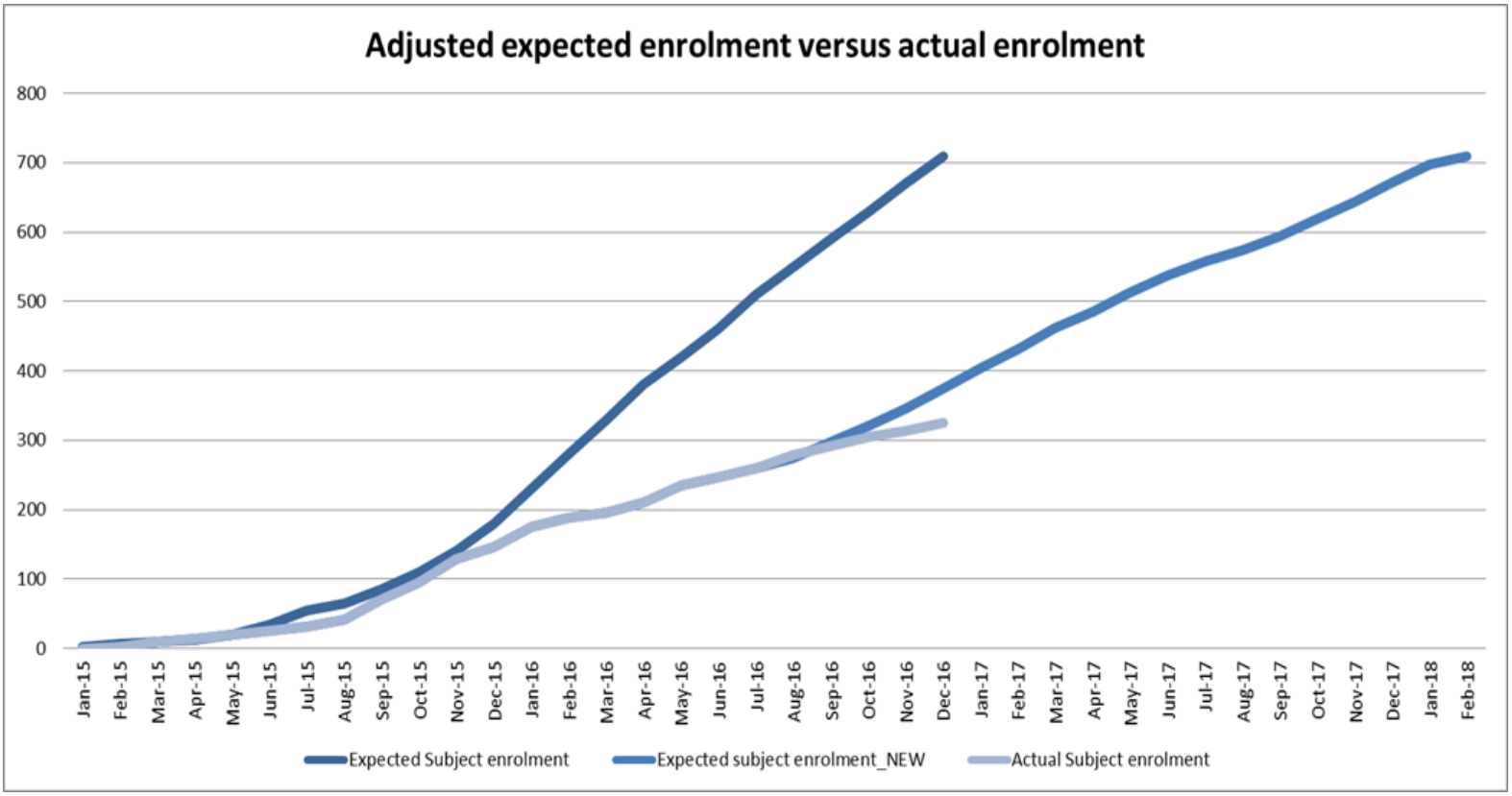


At this moment there are 42 sites actively screening for patients. Since the last newsletter many site included their first EULAST patient. We would like to congratulate all these sites with their first EULAST patient:

- Hradec Kralove– Czech Republic; Dr. R. Köhler
- Budapest – Hungary; Prof. I. Bitter
- Utrecht – The Netherlands; Prof. R. Kahn
- Lublin – Poland; Prof. M. Olajossy
- London – The United Kingdom; Dr. Dazzan
- London – The United Kingdom; Dr. Pappa

Despite the 325 included patients, **there is still a significant delay in recruitment.** The recruitment period has been extended within an additional year. In addition, the most difficult inclusion criteria (related to the duration of illness) has been broadened on request of many participating centers, **so we expect to see a much needed acceleration in recruitment in the next few months.**

According to our updated recruitment plan, 375 patients should be included at the end of this year. In the graph below both the previous and adapted enrolment goals versus the actual enrolment per month are displayed.



To meet our recruitment target we need to enroll 25-30 patients per month. In November, we did not reach this goal. We appreciate all the efforts that you are putting in this study, but we hope that we can increase the recruitment in the coming months, for the main study. We need your help in all of this and if we can assist you in any way, please ask your CRA!

Many sites already have exceeded their recruitment target of 5 patients per year and some are very near to their goal:

- Vienna – Austria; Dr. G. Psota
- Antwerp – Belgium; Dr. J. Luykx
- Sofia – Bulgaria; Prof. L. Hranov
- Dusseldorf – Germany; Dr. J. Cordes
- Munich – Germany; Prof. S. Leucht
- Munich – Germany; Dr. A. Hasan
- Athens – Greece; Prof. N. Stefanis
- Budapest – Hungary; Prof. I. Bitter

- Be'er Yaakov – Israel; Dr. M. Kupchik
- Jerusalem – Israel; Dr. A. Teitelbaum
- Pardesia – Israel; Dr. I. Oyffe
- Tel-Aviv – Israel; Prof. M. Weiser
- L'Aquila – Italy; Prof. A. Rossi
- Naples – Italy; Prof. S. Galderisi
- Turin – Italy; Prof. P. Rocca
- Trondheim – Norway; Dr. S. Reitan
- Santander – Spain; Prof. B. Crespo Facorro
- Oviedo – Spain; Prof. J. Bobes
- Kent – The United Kingdom
- Oxford – The United Kingdom
- Surrey and Borders – The United Kingdom

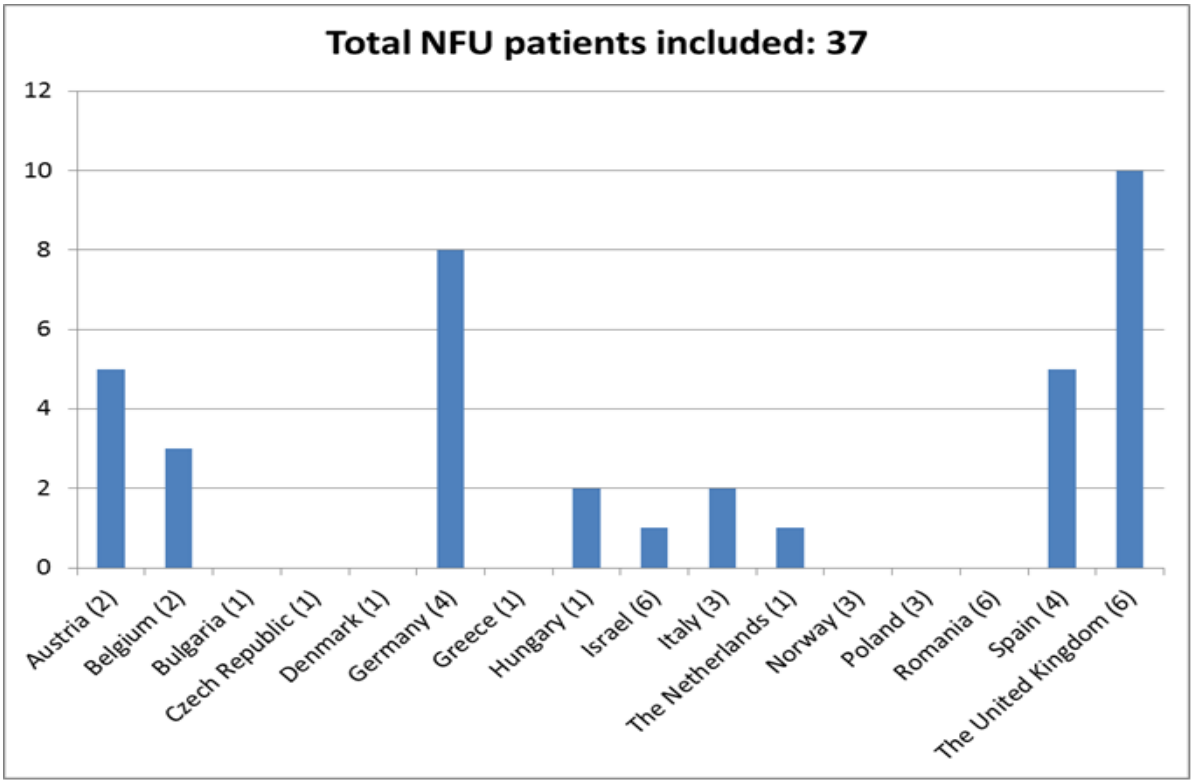
Some sites with less than 5 inclusions soon approach the end of their first recruitment year. These sites will be contacted by their monitor to discuss possibilities to improve recruitment.

Naturalistic follow-up

Recruitment

As mentioned in the study protocol, our aim is to include 150 naturalistic follow-up patients (refuser patients). Until now, 37 patients have been included within the NFU cohort. This means that we have a lack in NFU recruitment as well.

Please keep in mind the NFU part of the study and ask the patients if they are willing to consent for the NFU study, after declining the intervention study.



Protocol 3.0

In July 2016, protocol 3.0 was distributed. At this moment, this protocol version is approved at some sites and this has some implications. The most important implications are

- The inclusion period of the study is extended until February 2018. With this extension, we hope we can recruit the number of patients that we need. This means that we need 25-30 patients per month.
- Inclusion criterion: first contact with a healthcare professional is changed from 1-7 years to 6 months-7 years. Please make sure that you have all relevant documentation available in the patient file or in the source documentation. These documents are checked during monitoring visits. eCRF: once you have the approval for protocol 3.0, there are some changes applicable in the eCRF. This is for the main study and the NFU study. To enable the new protocol in the system, please make sure that you notified your CRA that you have the approval and send her the approval letter and the date. In addition, make sure that you have all patients that are enrolled in the study, entered in the eCRF. This is important because in this way the changes made for protocol 3.0, are only made in patients that are enrolled under protocol 3.0.
- Safety reporting is different in some situations. In protocol 2.0, only hospitalisations due to psychotic exacerbations could be reported to the sponsor with a delay of 30 days. With the approval of protocol 3.0, this delay is also applicable for hopsitalisations due to depressive symptoms and hospitalisations for social reasons. Please note that this is only a delay in reporting such events to us. This means that these SAE's still need to be reported! Reminder: SAE's can be reported within the eCRF system, so faxing is not necessary.
  Please note that this is only applicable if this is approved by your local authorities!

At various sites, the new protocol amendment has been approved and implemented. This has led to some questions relating to past risperidone exposure. Please note the following, related to protocol amendment 3.0:

- patients can participate in the study if they have a documented non-response or hypersensitivity to **one** of the study medications (that is, either aripiprazole or paliperidone/risperidone): the patient will be randomised to the **other** compound
- this means that a patient with documented non-response or hypersensitivity/intolerance to **risperidone** will be randomised to aripiprazole, as paliperidone is one of the active compounds in risperidone.
- the procedure of blocking one compound is also accepted for **patients who have experienced too many side effects** on one of the compounds (including risperidone) in the past, as documented in the medical file.

FAQ

- **Can patients switch from the NFU cohort to the main study and the other way around?**
  No, this is not possible. The intention if the NFU is to compare patients that refuse the main study with the patients in the main study. If we allow patients to switch between the two parts of the study, we cannot do that anymore. Therefore, it is very important to inform patients that they cannot be enrolled anymore in the main study later on, once they are in the NFU study.

- **If a patient is involuntarily treated during the study, does this patient meet ACD criteria?**
  If a patient is involuntarily treated during the study, one of the 'reasons for withdrawal' is applicable (protocol p. 35):
  The nature of the patients treatment is changed to involuntary treatment (based on judicial ruling). In case the duration of this involuntary treatment is no longer than one month continuously or three months cumulatively, the patient can be asked to reconsent and continue in the study, if this is permitted and/or required by local law.

  Involuntary treatment is not an explicit ACD criteria, so this situation will have to be indicated as the ACD 'clinician decision to withdraw the patient'.
- **Can we remind the patient before the visit that the next visit is almost there?**
  In normal daily practice, some sites are used to remind the patient **before** they have a visit to the depot clinic scheduled. This is allowed within the study, however, please note that the patients in the oral treatment arms should in that case **also** receive such a reminder, otherwise the depot treatment arms will be biased in favor of the primary outcome measure. You do not have to provide the patients with reminders if you do not do this for depot patients in normal daily practice. In short: if you provide a reminder in normal daily practice, you can do this for all participants. If you do not provide a reminder in normal daily practice, you should not do this for any participant.
- **What forms should I send to the central lab in Innsbruck together with the lab samples?**
  Only send the lab sample tracking logs (the list and the overview per box) together with the lab samples. In the lab guide there is mentioned that you should send an antipsychotic blood monitoring form, but this is not applicable.

EULAST study team

Some time has elapsed since the previous newsletter, we would like to give you an update on the members of the central study team.

1. Inge Winter, project manager
2. Leonie Willebrands, project manager
3. Lyliana Nasib, CRA, is responsible for Belgium, Hungary and the UK
4. Paula Ywema, CRA, joined our team, because she takes over Israel, Romania and Spain
5. Cynthia Okhuijsen-Pfeifer, CRA, is responsible for the sites in Austria, Germany, Italy, Norway and Greece.
6. Elianne Huijsman is a new CRA in our team.
   Elianne will be responsible for Bulgaria, Czech Republic, Denmark and Poland.

Final note

Then last, but not least, we wish all of you a very merry Christmas break and a happy 2017. We wish you and your families all the best on a personal level. Let’s keep up all the hard work in 2017 and make EULAST a big success.