Research Networking Programmes

Short Visit Grant ☒ or Exchange Visit Grant ☐

(please tick the relevant box)

Scientific Report

Scientific report (one single document in WORD or PDF file) should be submitted online within one month of the event. It should not exceed eight A4 pages.

Proposal Title: ENSAT-Monitoring Visit I - Germany

Application Reference N°: 6292

1) Purpose of the visit

In 2002, the European Network for the Study on Adrenal Tumor (ENSAT) was founded to achieve significant progress in Adrenal Tumors. As of today around 40 centers across Europe belongto ENSAT; moreover, a few centers oustide Europe (Brazil, USA, Canada) plan on joining the effort. The consortium deals with specific types of adrenal tumors: Pheochromocytoma/Paraganglioma (Pheo), Aldosteron-producing Adenomas (APA), nonaldosterone producing adrenocortical adenomas (NAPACA) and Adreno-cortical cancer (ACC). In order to enhance the established multicenter and international approach to clinical research, a virtual research environment (VRE) was developed.

The study for the Evaluation of Urine steroid metabolomics in differential diagnosis of Adreno-cortical Tumors (EURINE-ACT) is an ENSAT associated study and enrolls patients with ACC and NAPACA. The aim is validate a novel diagnostic tool for 1) accurate differentiation of malignant from benign adrenal tumors, 2) early detection of recurrency after an apparent curative adrenal surgery for ACC and 3) diagnosis of hormonal excess in adrenal tumor. The goal is to be able to prospectively enroll 2500 patients from ENSAT centers. The study will take 2 years with a calculated expected recruitment rate

of 80 patients per month. Up to date, more than 700 patients have been already enrolled with clinical data captured in the ENSAT registry and collected biomaterial sent to University of Birmingham for steroid metabolomics analysis. This allowed a centralized review of available data and biomaterial information.

The preliminary data review identified that a significant proportion of enrolled patients have discordance of data. This discovery led to development of a monitoring plan to improve the quality of the trial data and processes with the following outline:

1. Detection and characterization of problems by performing a selective audit of EURINE-ACT enrolled patients and stored biomaterial,
2. In depth understanding of identified problems in the data process and identification of new problems (both general and center specific) by in person EURINE ACT investigator staff visit to the best contributing centers,
3. Development and implementation of tools to better estimate data quality based on experience (1,2),
4. Reassess EURINE ACT data quality and participation.

In February 2014 the first part of the on site monitoring were visits to Germany. The University Hospital in Munich and the University Hospital in Wurzburg already recruited 243 patients (150 Munich & 93 Wurzburg).

2) Description of the work carried out during the visit

The monitoring was performed regarding GCP & FDA Guidelines and Guidance. In the health care sector to improve quality and in this case data quality, the Donabedian Model of the evaluation of quality was used. After a centralized monitoring where all data was reviewed (outcome), a site visit was scheduled to investigate processes and structures to find reasons for errors in the data. The general content was an interview with all local stuff, a source data verification and an overview of the biomaterial sampling for EURINE-ACT. For every site visit, one and a half days were scheduled to assess local processes and structures.

For the Outcome quality all flagged EURINE-ACT records were checked if they could be confirmed as EURINE-ACT. NAPACA and ACC records were assessed separately. For NAPACA the records needs to meet five criteria's (Imaging reference standards and biomaterial is available in the EURINE-ACT biobank), ACC records have to meet four criteria's (time when the biomaterial was collected, if patient received during this collection chemotherapy or mitotane and if the biomaterials is available in the biobank). Additional four mandatory NAPACA

registry items were monitored (Tumor size, DEXA Suppression test, Imaging performed and if CT is available, if HU are reported) and three ACC items (Tumor size, and for the case that the patients has no metastasis, surgery information and pathology information is available).

After monitored data errors were identified, a monitoring plan with an investigation of the reason for all critial items was developed. This monitoring plan was the frame for the assessment of the local data process and structure quality, which included: Checking of all Trial documentation (Source Data, Approvals, Documentation, Consents), an Interview with all local trial staff members to assess Protocol compliance, GCP compliance, training and delegation of duties and for the Data integrity a Source Data Verification (SDV) was performed. The SDV covered a re-abstraction of 7-10% records of the flagged EURINE-ACT patients. To avoid that the site is improving records, the ID from the records was given on the day of arrival. After the site visit a monitoring report will be provided to every visited site.

3) Description of the main results obtained

Munich 12/02/14-13/02/14

Outcome quality (data review)

Only 13% of all entered NAPACA records could be confirmed as eligible EURINE-ACT patients. In 28% no biomaterial was received and 59% do not meet the imaging reference standards that the data reviewer can judge if the tumor load is benign. The data completeness in the selected items showed, that more than 50% of the information is missing in each record, except of tumor size, which was mainly reported complete. The monitored ACC records showed an average data completeness of 75% but only 8% could be confirmed as eligible for EURINE-ACT.

Process quality

After the Patient is enrolled in the trial, the local investigator performs the data capture. Because of a huge workload the data capture and data entry could be done up to two weeks after the consent was written. After the Patients receive the informed consent they get referred to the local ambulance where they receive instructions how to collect the 24h Urine and information how the DEXA methasone test is performed. The patient returns the filled 24h Urine boxes to the ambulance, where it is aliquot to a 10ml tube. This tube will be send to the local technician, who prepares the tube regarding the EURINE-ACT SOP for the shipping to the biobank. The technician is using a local SOP that is similar to the EURINE ACT SOP

except a centrifugation before the urine get aliquot and frozen by -20 degrees.

Structure quality

To assess the structure all trial related facilities, where data was collected/entered and all staff members were interviewed. The ambulance, the consultant room and the laboratory was visited. The adrenal clinic in Munich performs around five clinical trials parallel to EURINE-ACT, six medical researcher and six trial assistants are involved in EURINE-ACT. The site confirmed an enrollment rate of 5-7 patients a month.

Evaluation

The largest identified problem were the confirmations of eligibility for the trial patients. Every staff member that is working on EURINE-ACT participated in the presentation of the data review. After the talk a discussion with the team and possibilities how to improve the quality of data were considered. During the discussion a problem was noticed, that the ENSAT-Registry works sometimes to slow, which is cumbersome for the data entry. Processes to decrease the server interaction delay are needed. To increase the data entry motivation a clear timeline for the trial flow was requested and after that it was provided by the trial manager.

The majority of all NAPACA Patients get referred from an external hospital to Munich. Some are eligible for an other study in the ENSAT-Consortium, which increased the work up with the patient. Some patients are not compliant if they have to sign more than two consents or have to visit the hospital for diagnostic procedures more than twice. Additional Munich recommends the Patient with a adenoma to visit the hospital after one year for a follow up visits. Some Patients don't follow that request. The local investigator noticed to improve the collaboration with the radiologist to enroll more NAPACA patients.

Summary

Munich is a high enrolling center for EURINE-ACT. The data showed that local staff members do not know what information for patient eligibility and mandatory items in the records must be entered. The importance of this items was shown and the needed outcome was discussed. All staff members ensured to improve the quality of the data regarding the requested criteria's. There was a high motivation of everyone to attempt the monitoring and to provide the monitors the requested information. With a implementation of a monthly quality report the data will be improved.

Wurzburg 13/02/14-14/02/14

Outcome quality

Wurzburg was identified as a center with a high enrollment rate for EURINE-ACT. From all entered NAPACA records only 4% could be confirmed as trial patients. For more than the half of all patients, no biomaterial was stored in the biobank. A third do not match the reference standards. Around 5% of all ACC records can be confirmed as EURINE-ACT. Biomaterial was received in a third of all patients and for 18% it is unclear when the biomaterial was collected.

Process quality

After the Patient is enrolled in the trials, the consultant fills out a general non-related trial CRF for the ENSAT-Registry. The local research assistant enters the data. Most of the ACC Patients get referred to Wurzburg after an adrenalectomy. Not in every case the patient provides a surgery or pathology report to the local physician. Most patients are not motivated to visit the site for a second time to return 24h urine. The local investigator noticed that only patients with Cushing's syndrome could be instructed to return on the next day. Since around 2011/2012 patients who underwent surgery in Wurzburg don't have good reported pathology report. No HU are reported in the majority of all CT Imaging reports. Additionally, the SDV showed that not every 3 month Follow-up was is reported in the eCRFs. Furthermore in every re-abstracted record mitotane and hydrocortisone therapy isn't entered in the Follow-up form. An attempt to perform a SDV in NAPACA patients failed, because no information in the selected patients (n=4) was entered. Some patients that are identified during the SDV are patients from Berlin. They were enrolled from Wurzburg in EURINE-ACT as part of a transfer from an other registry. But some patients are in the regularly check up in Berlin.

Structure quality

Seven medical researcher and three research assistants are involved in EURINE-ACT. One local research assistant is responsible for the data entry of ACC Patients. Temporary there is no researcher responsible for NAPACA patients, their data collection and data entry. Every facility is on the same floor of the adrenal clinic. The examination rooms, the hormone lab and rooms where the blood withdrawal and instructions for 24h Urine is performed were showed.

Evaluation

The majority of all trial staff members visited the data review report. In the following discussion some problems were reported. Examples are: some terms in the Imaging form must be better explained, there is a financial problem with the pathologist who supports the site with the pathology reports. The local investigator knows the problem with the NAPACA data entry, he ensured that the

information is already collected, but he will encourage someone to enter this information within the next two months. The best motivation for entering data is the biochemical report that could be provided to every ACC patient.

The research assistant mentioned that since 2011 very much changes are done in the eCRFs especially in the ACC Follow-up forms. There was no notice given to the sites, that additional items have to be filled out and it is distracting to enter imaging results in the Follow-up form and additional in a separate imaging form for NAPACA Patients.

Summary

Wurzburg has a very good overall data completeness in ACC records. But NAPACA records are poorly filled with information. It was ensured that this problem would be solved as soon as possible. Wurzburg and Munich have encountered the same problem with the pathology reviews. The local pathologist won't review the adrenal tissues accurate and the national wide centralized reviewer claims some additional fees for reviewing that can't be covered by additional funds. The staff members are highly motivated to improve the quality of data and they confirmed to further achieve a recruitment rate of 5-7 patients a month.

4) Future collaboration with host institution (if applicable)

Both institutes will further enroll patients for the EURINE-ACT study and focus of improving the data quality in regards to the data completeness. Munich, Wurzburg, Birmingham and other centers across Europe are part of highly visible and reputed Network dedicated to adrenal tumors. Their primary aim is not to be trapped in the data that is already collected in the ENSAT-Registry, but to extract information from data patterns and instead of dealing with this information, knowledge will be teased out to achieve significant conclusions in the treatment of adrenal tumors.

5) **Projected publications / articles resulting or to result from the grant *(ESF must be acknowledged in publications resulting from the grantee's work in relation with the grant)***

For the improvement of data quality with a data quality scores board in the eCRFs, ongoing sending of data scores and regularly scheduled video-meetings with the site, an article is planned for this summer. I/We acknowledge giving notice about the ESF grant in every resulting publication where data from this monitoring is used.

6) Other comments (if any)