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 III - Italy

Application Reference N°: 6371/6369

1) Purpose of the visit

In 2002, the European Network for the Study on Adrenal Tumor (ENSAT) was founded to achieve a significant progress in Adrenal Tumor research. As of today, around 40 centers across Europe belong to 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, NAPACA and APA. The aim is to validate a novel diagnostic tool for 1) an accurate differentiation of malignant from benign adrenal tumors, 2) an early detection of recurrence after an apparent curative (R0) adrenal surgery for ACC and 3) diagnosis of the 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 800 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 incomplete/low quality 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) and
4. Reassess EURINE ACT data quality and participation.

In April 2014 the third part of the on site monitoring was performed with visits of 4 main contributing centres in Italy: The University Hospital of Turin, University Hospital of Florence and the University Hospital of Padua.

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 when 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 critical 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 available 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.

3) Description of the main results obtained

Turin 01/04/2014

Outcome quality (data review)

The Center enrolled 48 ACC and 25 NAPACA Patients. The eCRFs showed an overall completeness of 76%, which is more than the total completeness of all centers. But as in all sites, there is a lack of information about imaging characteristics and size of the adrenal tumor. It is not comprehensible for an external reviewer, how the site classifies the tumor as benign or malignant.

Process quality

All other EURINE-ACT SOPs are related to the used procedures in the hospital. The Patients receive on the telephone an appointment; on the day of the appointment the consultant discusses the work up and refers him to the blood collection room. All mandatory blood is sampled. After two weeks, the patient appears again, receives the results and provides the ambulance with the 24h Urine Boxes. These boxes will be picked up by the research technician and will be transported to the laboratory, where the samples gets measured and analyzed. Before the shipment, the samples will be stored in the -20 degree freezer.

A local endocrine consultant performs data collection in the endocrine ambulance. All information is collected in the local digital health record. During the clinical care the data is transferred in the ENSAT Registry. This procedure is slightly different for NAPACA patients, where the data entry is performed on an afternoon, when a dedicated researcher has the possibility to access the registry.

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 were visited. The adrenal clinic performs around two clinical trials parallel to EURINE-ACT, two medical researcher, one dedicated resident physician and two research biochemist are involved in EURINE-ACT. The site confirmed an enrollment rate of 2-5 ACC patients per month.

Evaluation

The University Hospital of Turin is located in a suburb of Turin. It was a former center for tuberculosis. The adrenal center reported similar enrollment problems, compared to the other visited European centers. ACC Patient appears mostly after the surgery in Turin. Patient from all over the country schedule appointments with the adrenal consultant in Turin. Regarding public funding's an adequate research can only be provided for patients with cancer. Patients with benign tumors receive the standard care, but there is temporary no possibility for a researcher to enter information in the registry during routine care.

Every staff member who works with EURINE-ACT was present during the EURINE-ACT presentation. In Q&A session after the talk it was mentioned, that all members are motivated to enter more high quality data.

Summary

Turin is one of the most important adrenal cancer centers in Italy. With the presentation of the aims and procedures for EURINE-ACT, all staff members were motivated to improve the recruitment and the data quality. All problems that lead to low data quality are already noticed during the visits of the other centers. The governmental supply gives the advantage for a better research on cancer patients, but in the other hand, at time it is not possible to improve the recruitment of NAPACA patients. The local investigator is aware of these problems and is improving these circumstances.

Florence 02/04/2014

Outcome quality

Florence enrolled 12 ACC and one NAPACA Patient in the EURINE-ACT trail. In all ACC Records, no Imaging method or characteristic was selected. In the cases where surgery information was entered (n=10), reports about pathology are rarely entered (60%).

Process quality

Adrenal tumor Patients from all over Italy are can choose to be treated in Florence. The Patient visits the site three times. The first time to schedule the next appointments and to receive instructions for the next visit. During the second visit the blood withdrawal is performed and in the last visit the results are discussed and further check up is planned. One local resident physician is responsible for the data collection, data capture and data entry of ACC Patients. Like in other centers, are the majority of ACC patients referred after surgery to Florence. There is a good collaboration with the local pathology department, which provides the possibility to receive information about every patient that underwent adrenalectomy in the Hospital.

Structure quality

Four medical researcher and seven laboratory researcher are involved or deal with biosamples of EURINE-ACT Patients. Temporary there is no researcher responsible for NAPACA patients. The endocrine ambulance and the labor is not located in the same building. But the transport of the biosamples is well organized. The advantage of EURINE-ACT is, that it doesn't need any additional information that is not collected during clinical care.

Evaluation

The local investigator reported problems with the local ethic department, who slow down processes for the enrollment of trial patients. Additional human resources for clinical trials are difficult to recruit. All mandatory items were discussed with the dedicated resident physician and the local investigator. It was noticed that information about Ki67 and Weiss Score is not complete entered, the local investigator confirmed an improvement in that items. There are resources for NAPACA biosamples from Patients that are already sampled. The prospectively enrollment of will be still problematic, because the local regulation do not allow additional work up or time for research interests in benign tumors.

Summary

Florence is a highly motivated research center. Their focus is in basic research. Two clinical trials are performed in the adrenal center. The site was reminded to increase data quality in imaging and pathology reports of their entered records. Florence showed a high motivation to improve the prospective enrollment of benign and malignant lesions and the process of high quality data.

Padua 03/04/2014

Padua entered two EURINE-ACT patients in the registry in November/December 2012. No centralized monitoring was performed, because no general trend of data could be detected.

Process

During the site visit the data process of data collection, data capture and data entry was discussed with the local researcher. A dedicated endocrinologist will prospectivly enroll ACC Patients. Some NAPACA Patients can't be seen by the researcher, because there is no information given from other physician within the hospital.

Structure

Two clinical researchers perform the clinical care and three basic researchers are involved in biosamples of EURINE-ACT patients. The research laboratory and the endocrine ambulance are separated from each other. Similar to the other Italian centers, two clinical trials are performed in the adrenal clinic. There is a possibility to hospitalize ACC for one day to schedule all diagnostic procedures.

Evaluation

Because of local limitations in regulations and human resources, an enrollment of more EURINE-ACT patients couldn't be performed until the site visit. The center noticed that there is a possibility to enroll retrospective ACC patients for EURINE-ACT from 2013. During the talk and in the discussion the EURINE-ACT trial manager showed the benefit and simplicity of the trial to collection information during the clinical work up. An collection form was provided to the site to support the data process and increase the data quality.

Summary

The site visit was performed to investigate local processes and to initiate the study on the site. All procedures to prevent the collection of low data was discussed. Staff members of the site visited the presentation and a high motivation for an improvement of the enrollment of trial patients was confirmed.

4) Future collaboration with host institution (if applicable)

All institutes will further enroll patients for the EURINE-ACT study and focus of improving the data quality in regards to the data completeness. Padua, Florence and Turin are part of the institutes that have initial driven the founding of the ENSAT-Consortium. This italian centres, Birmingham and other centres across Europe are part of this

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)