

Trip Report: Belarus Thyroid Study

March 6 – 11, 1999

Daniel J. Fink, M.D.

A. Summary

The project continues to screen at a rate of about 600 subjects per quarter. This has occurred in the context of the ongoing move and renovation of facilities in the new Dispensary. These facilities will be completed over the next month or two.

The pace of laboratory testing has picked up since the last visit but there were significant problems with the RIA testing (see below). Results were generated for all patients from the 2Q of 1998 through the 1Q of 1999 except for 1Q 1999 antibody testing which is awaiting the next shipment of reagents. However, little progress has been made on the backlog before the 2Q of 1998, perhaps due to an under-requesting of reagents.

The laboratory has implemented the Quality Control procedures that were presented on my previous visits although the usage of these procedures needs to be improved.

There were significant problems with the RIA testing for anti-TPO and anti-TG. These problems were probably due to the use of expired RIA kits that have a shelf life of only 6 weeks. These problems necessitate repeating some runs of anti-TPO and anti-TG and verifying the accuracy of other runs. TSH and Ionized Calcium results seemed to be acceptable.

I met with Dr. Olga Polyanskaya who seems to be effectively taking charge of Quality Control for the project. She expressed several concerns that should be discussed during the visit of Dr. McConnell and Dr. Robbins later in the month. Briefly, Dr. Polyanskaya is concerned about the development of private databases by various groups in the project. She also feels she needs more computer support. She would like to discuss the data collection forms in order to ensure that they contain enough information to link specific forms to the correct screening visit. She would like some guidance on how to prepare a Quality Control manual. Finally, she would like to discuss how to resolve discrepancies in diagnoses between various sites or stages in screening and which level of final diagnosis is the "final diagnosis," i.e., clinical, surgical, pathological, etc.

B. Recommendations

Belarus Trip Report: March 6 - 11
Fink

D.

All immunologic testing should be changed to Brahms' reagents. This will eliminate the short half-life problem of RIA kits and the difficulties in acquiring Abbott reagents. This will also mean that the Belarus project will be using the same testing methods as the project in the Ukraine, making the results more comparable.

During or shortly after the installation of the new instrument, Dr. Mincey should visit the laboratory to make sure they get off on the right foot in using the instrument properly. This would ensure the proper evaluation of the new instrument and hopefully prevent the need to repeat any testing due to poor procedures.

The laboratory should improve Quality Control Procedures by running more controls and recording corrective actions when controls are out of range. Control levels should not be omitted to save money. They have agreed to do this.

The problem runs must be repeated and samples from other runs tested with expired kits should be repeated to see whether these runs should be re-tested as well.

Dr. Polyanskaya should be given training on how to enter and extract data from the DCC database and advice on how to use this database as part of her Quality Control procedures. The need to maintain data centrally and the use of the central database needs to be discussed with the Belarussian project team.

Issues with forms need to be reviewed.

Advice on how to set up a quality control manual (with examples if possible) should be given to Olga.

Belarus Trip Report: March 6 - 11
Fink

D.

C. Trip Narrative

Monday, March 8, 1999

Meeting with Dr. Petrenko in the laboratory

The laboratory is still located in the building under renovation near the new dispensary. The finishing touches are being made to the laboratory space in the dispensary and the laboratory will move to the dispensary in a few weeks. On a sad note, about two weeks ago, one member of the laboratory staff collapsed and died while at work in the laboratory.

Dr. Petrenko and I reviewed the progress of the screening and laboratory testing. About 600 patients were screened in both the third and fourth quarters of 1998 and about 400 patients so far in 1999. The progress of the laboratory testing is summarized in the table below. Little has been done with the backlog because of the unavailability of reagents.

Time of Screening	Ionized Calcium	Urinary Iodine	TSH	Antibody to TG and TPO
2 Q 1998	Completed	Completed	Completed	Completed
3 Q 1998	Completed	Completed	Completed	Completed
4 Q 1998	Completed	Completed	Completed	Completed
1 Q 1999	Completed	Completed	Finish by 3/13	Pending

The Ionized Calcium measurements are usually completed the day the specimen is collected or received from the mobile team. The urinary iodine measurements are completed within one week of collection. The TSH and antibody tests are performed on roughly a weekly schedule when kits are available.

Shipments of TSH kits from Abbott were received in May (800 tests), October 25 (1600 tests), and on December 30 (1600 tests); about 1000 TSH tests remain. Shipments of Anti-TG and Anti-TPO kits were received in August (1000 tests) and January (1000 tests); these reagents have been used up and testing can not continue until more kits are received. A memo was sent to Dr. Masnyk on 2/4/99 requesting more supplies.

Two general problems with testing. First, the gamma counter interface is broken so coated tubes are taken to Aksakovchina for counting. Second, the RIA kits have arrived with a very short period of time left before expiration resulting in most assays being done with expired reagents. The review of QC data (see below) showed that this was a significant problem. Reporting of results is delayed until all

Belarus Trip Report: March 6 - 11

D.

Fink

testing on a patient is completed because the clinical group does not want to receive partial data, as final diagnoses are not made until all the data is available.

After completion of testing, data is kept in four places. First, the data is entered into a Paradox database designed, programmed, and maintained by the laboratory. Second, the data is entered into an Access database (designed by the DCC) residing on a laboratory PC; this data is copied to a floppy disk and delivered to the DCC for entry into the project database. Third, the data is entered onto the project forms; when the forms are completed, they are sent to the clinical group in the dispensary. A computerized list is sent with the forms and the clinical group uses this computerized list because it is easier to find data. Finally, a log of all results organized by patient is kept in a laboratory notebook. This system seems redundant.

Tuesday Morning and Early Afternoon, March 9, 1999

I reviewed Quality Control and test results with Dr. Petrenko in the laboratory.

Anti-TG: Review of Quality Control showed that the QC for the run of 11/29/98 was out of control. We reviewed the raw data from that run and found that the total counts (B_0) were much lower than for other runs. There were three possible reasons for this. First, the RIA kits have a shelf life of six weeks with an I^{125} half-life of 45 days. The kits used on 11/29/98 had expired on 8/6/98. Thus, the total counts were well below that considered acceptable for the kits. Second, the counter used was different than the one used for the other runs. This counter seems to have a lower efficiency, also contributing to lower total counts. Finally, the temperature in the lab was measured to be below the official operating range for the test. All these factors, documented by the out of control QC values, indicate that the run of 11/29/98 must be repeated. More problematic is the data obtained from other runs where the kits were expired; the QC for those runs is acceptable but the total counts were low and the environmental conditions are unknown. This data is probably acceptable but a subset should be repeated to demonstrate the acceptability of the results.

Anti-TPO: Review of Quality Control again showed that the QC for one run (11/12/98) was out of control at both levels and the QC for the run of 2/25/98 showed one point out of control and the other with poor precision. Again, the analyses were conducted with expired kits, performed using the low efficiency counter, and subject to uncertain environmental temperatures. Both these runs need to be repeated and the runs using the expired kits need to be sampled to see if they should be repeated.

Ionized Calcium: Review of the Quality Control showed two points out of control. These represented problems with the instrument, which resulted in replacing and reconditioning the Ionized Calcium electrode. The controls were re-run and were

Belarus Trip Report: March 6 - 11
Fink

D.

acceptable but the new data were not entered on the control charts. I recommended that corrective actions be recorded in writing and that the repeat QC data should be entered onto the control charts. The rest of the data seemed acceptable. However, they were running only one level of control; the second had either been put away during the move or had run out. They have agreed to run two levels of control when a second level is available.

TSH: Quality Control was acceptable for this analyte although the controls were not being run with the frequency recommended by Abbott. The laboratory was only running two levels daily instead of the three provided. I pointed out this requirement and they will begin running three levels each day. Also, Abbott requires that a control be run with each group of tests; the lab was doing this but running only the middle control each time. I recommended that they alternate between the control levels in order to monitor what was going on at all parts of the standard curve. This is not essential but they agreed to do this.

Late Tuesday Afternoon, March 9, 1999

Dr. Petrenko and I went to the dispensary late in the afternoon to look at the new screening center. The area is still under active construction but some parts have been completed and are in use. The reception, interview, and endocrine areas are completed. Ultrasonography is still being done upstairs. The laboratory area is a few weeks away from completion. The hallway still needs a great deal of work but could be completed in a few weeks. The completed rooms are brightly lit and are better than most of the facilities I have seen there. The lab space is a little small but should be acceptable.

Wednesday Morning, March 10, 1999

Met with Dr. Stezhko and Dr. Petrenko at the Institute on Masherova Street

We discussed the problems with the laboratory testing and that I planned to recommend that we switch over to Brahms chemiluminescence reagents in order to avoid the problems with shelf-life and gamma counters. He wanted to know when the changeover to new reagents would take place. I explained that Dr. Masnyk would need to approve the request and find the funds but that I felt it could be done quickly given the resources. He asked me to tell Dr. Masnyk that tests can not be done without reagents.

Dr. Stezhko described the progress of the project. It has been difficult to screen because of the moving but the work continues. They are concentrating on looking for high dose patients and using mobile teams to screen where people live. The screening teams have made three trips in the first quarter resulting in 400 people

Belarus Trip Report: March 6 - 11
Fink

D.

being examined. They have started publicizing the project using radio and print advertisements that have just started appearing in local newspapers.

Dr. Stezhko feels they need four screening teams: one in the dispensary, two teams to alternate going to the rayons, and one team in Gomel. The project needs two more ultrasound instruments that travel well, although not immediately. The project needs working instruments and reagents delivered on a regular basis to function smoothly.

Met with Dr. ?? and Dr. Petrenko

I had a brief meeting with Dr. ??, the new director of the institute. He basically just said hello and asked me what was my position back in the United States. His main concern seems to be to find a new home for the institute and DCC, as this seems to still be unsettled.

Met with Dr. Olga Polyanskaya and Dr. Petrenko

Despite several imminent moves, the DCC was still in the Masherova Street location. The DCC is supposed to move within the next two weeks but this move has been imminent for some time. After packing up the DCC in anticipation of an earlier move and then doing nothing for a week, the DCC staff has unpacked some of the computer equipment and resumed working.

Dr. Polyanskaya seems quite committed to the quality control process and has made several useful efforts. With a little assistance, she should be effective in this position.

The delay in getting laboratory data is slowing the project. She is refusing to allow final diagnoses without the laboratory data, particularly the antibody results required to resolve the issue of thyroiditis. The results on 700 patients from the fourth quarter were delivered a week ago on diskette and are in the process of being added to the database.

The staff of the DCC consists of only one full-time programmer and two half-day programmers. She did not consider this adequate.

Clinical data is entered at the dispensary and then sent to the DCC on disk where it is entered into the database. There is no QC of this data prior to receipt at the DCC. QC is being done after receipt in the DCC but it is done manually. I think that Olga needs more computer support and needs to be taught how to access the database to sift it for inconsistencies and information. Both she and the DCC staff should be encouraged to help her acquire and use these skills.

Belarus Trip Report: March 6 - 11

D.

Fink

They are having troubling linking visit, lab, and clinical data together because there are no dates on the lab sheets and sheets reported back from Aksakovchina. She thinks the forms should be changed (e.g. hospitalization, cytology, and laboratory). If results and consults came back immediately, this might not be a problem. Also, the Cytology form does not indicate which specimen the diagnosis is from, the date, where done, and how many pieces were reviewed. I did not have time to review the forms to confirm these problems but I think the clinical group should explore these issues during their upcoming visit.

Olga has been correlating biopsy results from the dispensary, Oncology Center, and Aksakovchina. She has gotten them to let her cytologist (dispensary I think) review the data and has brought them together to resolve differences. There was only one case where agreement could not be reached. In some cases, staging was different because they may have been looking at different fields. The forms do not record how much tissue was taken versus how much was received or reviewed. The links of other pathologists to the project are weak. Results are delayed

She is concerned about how data is being extracted and shared by the study team; various groups are keeping private databases. For example, the Epidemiology group is extracting data from the clinical forms, not from DCC database. The lab is also keeping its own database. If Olga makes a correction to the database and forms, these changes are not reflected in the Epidemiology data. Conversely, changes made by others may not be conveyed to the DCC database.

Olga has been reviewing diagnoses for consistency between dispensary clinicians, cytology, oncology center, and Aksakovchina. She has also been looking for discrepancies and missing data. She wants to discuss the issue of the level of verification of diagnosis and which diagnostic levels will be correlated with outcomes. Different diagnostic levels are screening, biopsy, endocrinology in dispensary, surgical, and pathomorphology. Which diagnosis will be used and how does she reconcile differences among these in the database.

Olga would like to see an example of a QC manual to use as a model.