IFCC Working Group on Standardization of Thyroid Function Tests (WG-STFT)
Meeting at AACC 2011, Atlanta, GA, Monday July 25th (2:00 - 5:00 pm)

PARTICIPANTS

The meeting attendance list is attached in annex 1.

OPENING OF THE MEETING

The chair welcomed the meeting attendees and proposed to make a roll call. She continued with a presentation of the meeting agenda and expressed her regret that no results of the Phase III study were available for discussion. As known, this was caused by a delay in sample procurement (to be discussed).

OBJECTIVES OF THE MEETING

The chair explained the objectives of her presentation:

- Give a status update
- Explain the planned transformation of the IFCC WG-STFT into a committee
- Discuss topics related to the data of the Phase I through III studies, such as:
  - Anonymous data reporting
  - (In)Appropriate use of data and papers
  - Position of WG for Phase III and future
- Establishment of the physician/laboratory interface.

STATUS UPDATE

IFCC international conventional reference measurement procedure for serum free thyroxine
It was with great pleasure that the chair announced that the IFCC international conventional reference measurement procedure (RMP) for serum FT4 has been approved by the IFCC SD and EB. The manuscript (currently available as epub) will be published in *Clinical Chemistry and Laboratory Medicine*. In parallel, the FT4 conventional RMP has been submitted to voting by the National Societies, full member of the IFCC (deadline: 31/08/2011). The chair regretted that maybe it took more time than desirable before the FT4 conventional RMP could be finalized, but explained that finding a 2nd laboratory for transfer of the UGent method had been prohibitive to a speedy process. She expressed her gratitude to Dr. M. Umemoto, Director of the Japanese reference laboratory of ReCCS, for his contribution to bringing the required transfer study to a good end.

Phase II study: additional experiments on TSH immunoassay performance on clinical vs euthyroid samples
The chair recalled the striking observation in Phase II (2009), more specific the different behavior of certain TSH immunoassays when measuring clinical (TSH concentrations >10 mIU/L) vs euthyroid samples. The cause was unknown up to now. One hypothesis was that it could be due to a difference in specificity of the assays' antibodies to thyroid disease state-specific glycosilation patterns. She recalled that her laboratory had performed in this context a 1st experiment (2010), in which 2 assays (showing the different behavior in Phase II) measured clinical (TSH concentration >10 mIU/L) and euthyroid samples (n: 30/30), all obtained from the same hospital and analyzed in the same run (2 repl., & at random). This experiment did not confirm the Phase II observation. Because of a 2nd hypothesis that in Phase II maybe samples from patients treated with recombinant TSH had been included (despite this was an exclusion criterion), a 2nd experiment was performed. The same 2

assays as in experiment 1 measured samples from patients treated with recombinant TSH (continuum of concentrations >10 mIU/L) and from euthyroid individuals (n: 30/30) (sample location/collection and measurement protocol identical as 1st experiment). Again, the Phase II observation was not confirmed. The chair concluded that probably the reason for the different behavior of certain immunoassays in Phase II would never be found. None of the attendees had an explanation or suggestion for additional experiments.

Phase III study

The chair recalled that an order had been placed for the Phase III study to the company Promeddx, i.e., 100 clinical samples for TSH and 90 for FT4 (3 categories: eu –, hypo – and hyperthyroid). Unfortunately, the last update on the status of collected samples demonstrated the difficulty of obtaining samples categorized as above. In reaction to this, there had been consultations of the chair with Dr. Jim Boushell (Promeddx) on how to solve the problem. One solution had been the WG-STFT to agree that treatment would be omitted as exclusion criterion. In addition, Promeddx proposed to search new clinical centers, which required, however, a higher budget. The chair agreed to bear the cost increase but set the deadline for sample collection to October 31, 2011, since it was unsure whether the concessions would significantly speed up the process.

To further illustrate the difficulty of establishing an infrastructure for clinical samples (which by the way not only applies to the project of the WG-STFT but also to all other standardization/harmonization projects), the chair told about her experience with Dr. Greg Miller, who kindly offered help for collecting samples in collaboration with the clinicians in his hospital (coordination/aliquoting would be in the hands of Promeddx). Unfortunately, after the preceding necessary negotiations, clinicians suddenly withdrew their involvement, because it would cause too much of an additional workload. Therefore, the chair searched and contacted 2 other companies for potential provision of clinical samples, i.e., SLR Research Corporation (USA) and Invent Diagnostica (Germany). She even placed, by way of pilot investigation, an order to SLR for several clinical samples for TSH and FT4. These samples will be sent to her lab in Gent in the near future. One of the attendees asked to verify that SLR obtains the samples in the US rather than in countries like South-Africa etc., and if so, whether they follow the usual ethical rules. Meanwhile the chair had her promised face-to-face meeting with the project leader of SLR. The reply on all above questions was favorable (see documents in annex 2). The chair will wait until the deadline (October 31, 2011) imposed to Promeddx, before placing any further order. This will of course require electronic consultation with the WG members/participants.

There was a question for clarification about the volume needed for the clinical samples. The underlying idea was that some countries (e.g., in the UK) have established networks of clinical laboratories that can store "interesting" clinical samples in small volumes (1 mL). The needed volume per donation for Phase III is 15 mL of serum (~ 30 mL of blood) per patient. This precludes of course the help of clinical laboratories, unless pooling would be allowed. The chair emphasized that low volumes of single donors do not serve the purpose of the WG, because it requires all manufacturers to measure the same samples in order to get an objective estimation of their assays' performance, and also to assess the feasibility of the TSH harmonization approach based on the all laboratory trimmed mean. Everyone agreed on this. It was also questioned whether the extreme concentrations of TSH (at the low and high end) really are needed, since it is known that samples in these categories (especially the lowest TSH samples) are difficult to collect. One of the attendees replied that the FDA requires that standardization covers the full measurement range claimed for an assay. It was stressed in addition that the distribution of the samples' concentrations in the

different categories should be reasonably symmetric. Another reason for including a minimum number of samples covering the high and low range typical for thyroid disease is because the component that immunoassays measure may differ among procedures (in particular for TSH, assay antibodies may recognize TSH with glycosilation patterns typical for hypo – or hyperthyroidism differently). The chair agreed by saying that this was exactly the reason why, in contrast to the Phase I and II studies that mainly comprised euthyroid samples, the Phase III study has to include samples covering the eu –, hypo – and hyperthyroid status. The discussion returned to the difficulty of collecting clinical samples with extreme concentrations. It was proposed whether it would be worth giving supplementation and/or pooling of clinical with euthyroid samples a chance, to serve as alternative to more quickly obtain the samples. The risk is of course that pooling weakens the characteristic of a sample with a concentration typical at the extreme concentration ranges. The chair responded that for her this would be the very last option, which would, in addition, require thorough investigation of commutability of the pooled samples. She recalled that by courtesy of M. Rottmann (Roche) 3 pooled/supplemented samples were awaiting (stored at -70°C) to be included in the Phase III study. The WG indeed decided last year to investigate the potential of using a restricted number of supplemented pools to cover a broader measurement range than usually available directly from patients. One attendee came back to differences in glycosilation pattern of TSH in the upper range, which would potentially cause big scatter of results in that range. Eventually this feature could hamper the feasibility of the investigated harmonization approach based on the all procedure trimmed mean. Someone added that, because thyroid hormone assays (in particular TSH) are in the top 5 of bestselling assays, the feasibility should be very well investigated, again a reason for all assays to measure the same samples. This statement found general consensus and closed the discussion about sample procurement.

TRANSFORMATION OF THE WG-STFT INTO A COMMITTEE

The aims for the transformation of the WG-STFT into a committee are to prepare the implementation of standardization, to involve a broader forum of stakeholders and to accomplish the commitment of the stakeholders to standardization. This transformation, which will require writing of adequate mission statements, will be prepared by the current WG-chair and the IFCC SD-liaison (L. Siekmann) before the end of 2011.

SELECTED DISCUSSION TOPICS

The chair tackled some selected discussion topics (see below).

Anonymous data reporting – Position of WG for Phase III and future

The chair recalled that anonymous data reporting had first been permissible for the 3 publications in *Clinical Chemistry* (Part 1 – 3 on TSH, FT4/FT3 and TT4/TT3, respectively) and in *Clinical Chemistry and Laboratory Medicine* (Status report), however, that after publication, the editor of *Clinical Chemistry* (N. Rifai) asked to disclose the results of the different manufacturers. G. Beastall mentioned that actually he had been asked as IFCC president to take position on this, but that he referred to the IFCC corporate members and diagnostic trader associations. Although these recognized that assay disclosure is helpful to the scientific community, they considered that the decision to disclose or not is governed by the objective and the phase of the study. Simultaneously, the WG-STFT chair was asked to consult with her project colleagues, but, finally could not comply with N. Rifai's request to disclose the data a posteriori. In her reply she referred to her earlier taken commitment to industry, who also showed big commitment to the project objectives by upfront sponsoring of

the past (Phase I and II) and future (Phase III) studies. Consequently, N. Rifai published an editorial in *Clinical Chemistry* together with a consortium of laboratory medicine journal editors, and called for future "full disclosure" of industry-sponsored laboratory medicine research studies. The liaison between the WG and the IFCC SD (L. Siekmann) continued the discussion by stressing that disclosure is not only required by the above consortium, but also by the IFCC SD (recall: last year the issue was discussed in the presence of I. Young (before vice-chair, currently chair of the IFCC SD), who also was in favor of disclosing the data). One of the manufacturers' attendees commented that he did not understand the editors, because there was in the 3 papers disclosure of the project participants. In addition, it was clear to him that there was misunderstanding on the WG activities in that they were not about a simple method comparison, but about a study of the technical feasibility of standardization or harmonization of FT4 and TSH measurements, all with as primary goal the improvement of thyroid function tests. In addition, he referred to the fact that CAP and external quality assessment (EQA) surveys also do anonymous reporting. L. Siekmann argued on this and referred to EQA schemes that fully disclose assays.

With regard to standardization/harmonization/disclosure, it was mentioned that alternatively sharing of antibodies by all manufacturers could serve as plan B. This alternative approach was immediately argued, since it had not been successful for hCG.

With regard to disclosure of the next Phase III study, some considered it part of the earlier agreement on anonymous reporting; others would agree to full disclosure under the condition that the manuscript can again be reviewed by the participating manufacturers, while others preferred to only disclose after standardization has been achieved. On the other hand, it was recognized that if the Phase III study would make obvious that tests measure different quantities, disclosure would be necessary, because then results would need to be differently interpreted. Conclusion: since there was no consensus to disclose the data of the planned Phase III study, the report on the Phase III study will be kept anonymous, even when it risks to be refused for publication. In reply to this, the chair mentioned that the Phase III data could be shown in a report on the IFCC website. She proposed that for the forthcoming studies (e.g., the one implying the real standardization step), the disclosure/publication issue would be discussed again. With regard to standardization, a clear caveat was expressed: the step towards standardization should be set simultaneously by all manufacturers to prevent confusion from standardized vs non standardized assays in circulation. In this regards the chair was asked to take care of having representatives from regulatory bodies (e.g., the FDA) in future meetings. This is particularly needed in view of the implications to expect after standardization or harmonization of FT4 and TSH assays. Indeed, the processes may face manufacturers with the requirement of a new FDA clearance. The chair agreed to contact the FDA (e.g., by inviting her previous contact A. Gutierrez) after the results of the Phase III study would be available. At this point an attendee came back to the difficulty of the standardization process to cover an assay's full measurement range. He indicated that the inclusion of supplemented pools (instead of native samples) in the standardization process would also need approval by FDA. In this context, the chair recalled that in the last meeting, A. Guttierez had questioned the need of those broad measurement ranges. One of the manufacturers' representatives mentioned that the measurement range is considered a competitive element, and even though in practice extreme thyroid hormone concentrations are seldom found, manufacturers are not willing to cut back ranges, when others don't.

(In)Appropriate use of data and papers

The past and future studies should not be used as a marketing tool. One attendee recalled the agreement among manufacturers to not disclose their assays to customers, which, according to his information, had not strictly been respected by all colleagues. Another attendee added that it was the policy of his/her company to describe the work of the WG-STFT to customers, without disclosure of their own data. This was considered a proper strategy by all attendees/manufacturers' representatives. The chair asked the manufacturers' representatives to convey this message within their company.

Establishment of the physician/laboratory interface

The chair recalled that since January 2010 the WG looks to actively involve clinicians for many reasons (sample repository; support for implementation of standardization or harmonization, etc.). Although several clinicians immediately declared their interest, they finally did not join the activities (cf. sample procurement). The chair recalled her contact with W. Rosner (JCEM) who is working together with CDC on standardization of testosterone. He invited her to write a paper for JCEM, with the aim to describe what is wrong with thyroid function testing. When she submitted her manuscript (shared with 2 Belgian endocrinologists from the University Hospital of Brussels) entitled "Improving the measurement of thyroid hormones – Importance of the physician/laboratory interface" to W. Rosner, he thought that, although the plea for collaboration with clinicians was justified, it came too early and needed discussion in a face-to-face meeting with the chair. This happened meanwhile. His idea is to restrict in a first phase to evidence of what the issue with thyroid function testing is (he referred to his previous position paper on the problems with testosterone testing). He then would solicit a thyroidologist in the Endocrine Society to maybe join the paper or write an editorial to call upon involvement of clinical stakeholders. The chair will look what she can do.

Then the way on other means for the WG-STFT to come into direct contact with physicians was discussed. The chair referred to the approach used by the AACC Harmonization Task Force (see www.harmonization.net), i.e., take on board from scratch all possible stakeholders (as done in the inaugural meeting in Oct 2010. The attendees agreed about the importance of urgently establishing a relationship with clinicians, but commented that the clinical chemistry community will have to go to conferences of clinicians, since the latter will never attend conference dealing with laboratory medicine topics. Most adequate would be to receive the opportunity to organize satellite to or in a clinical symposium a workshop dedicated to the WG-STFT objectives/activities. Someone referred to a similar strategy used by the Japanese Thyroid Association on occasion of a medical symposium. They had invited him as manufacturer representative and the chair of the WG-STFT to give a presentation to an audience mainly of edocrinologists/clinicians. The chair told that also in her own country she succeeded in being invited to give a presentation in the annual meeting of the Belgian Thyroid Club. The chair asked G. Beastall (IFCC president) to introduce the WG-STFT to the British and European Thyroid Association, which he agreed to do. It is to hope that also the American Thyroid Association will follow this initiative.

OTHER BUSINESS

Anticipated timelines for the Phase III study – Location of meeting to discuss the Phase III outcome

Provided the samples will be available in fall 2011, the chair proposed to measure the samples early 2012. The meeting could be held in Ghent (BE) again, however, in view of the continuous restriction of budgets for traveling, it was considered best to have meetings satellite to one or the other laboratory medicine symposium. Hence, it was agreed to discuss

the report of the Phase III study in 2012 satellite to the AACC annual conference in Los Angeles (CA). It was stressed that the discussion would only make sense after assembling of all data.

Other items

L. Siekmann asked to compare the data of the method comparisons with those obtained in EQA surveys, however, manufacturers' representatives questioned that EQA samples are appropriate materials. L. Siekmann replied it would be the aim to investigate on an anonymous basis whether companies perform in a similar way on EQA samples as on native samples, in other words, indirectly whether EQA samples are commutable.

Someone asked whether meanwhile a reference measurement procedure for TSH based on mass spectrometry has been developed (he actually thought that C. Ronin was doing this in her spin-off company named Siamed'Xpress). The chair replied that she thought that C. Ronin's aim with Siamed'Xpress rather was to develop a new TSH immunoassay dedicated to early detection of hypothyroidism, in other words, an immunoassay specific for the glycoforms typically found at the onset of hypothyroidism. Anyhow, C; Ronin announced that she will be organizing a workshop in Marseille (spring of 2012) to explain her R&D work objectives. It was questioned but not really answered whether it would be worth for the WG to wait for this research.

CLOSURE OF MEETING

The chair thanked the audience for their contribution to the rather brief meeting.

Annex 1

Name	Affiliation	e-mail address
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Minutes made by:
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BioMed·IRB

IRB Meeting Date: June 24, 2011 **Expiration Date:** June 7, 2012

BIOMED IRB CONTINUAL APPROVAL NOTIFICATION

Study Title: A registry for collection of data, and repository of Clinical Specimens "serum, plasma, body fluids and tissues".

Sponsor: SLR Research

Protocol Number: 06012006

Protocol Dates: Amendment No. 1 dated June 8, 2006
Amendment No. 2 dated October 11, 2006

BioMed IRB has approved the above referenced study as having satisfied the criteria for continuing research at the June 24, 2011 meeting. This approval is effective from June 7, 2011.

The IRB committee has determined that the risk assessment for this study is Minimal. The IRB has determined that continuing review of this study will occur annually.

Approximately thirty days before June 7, 2012, you will be required to complete a Continuing Review Report Form. Continual review is the responsibility of the Sponsor. If you do not receive this form, please contact the IRB office immediately. The Continual Review Report Form must be received by the due date to allow ample time for ongoing review before the study's expiration date.

IRB approval is granted conditional on your adherence to the following requirements:

- The information submitted to the IRB is true and correct.
- Research will be conducted in accordance with the approved protocol.
- All materials used to recruit study subjects must be pre-approved by the IRB.
- Additional safeguards will be followed when vulnerable subjects, such as children or minors, are participants in the study.

The sponsor agrees to report the following information to the IRB:

- Serious Adverse Events (IND Safety Reports) occurring at any site should be reported no later than thirty (30) days from the date of discovery.
- Any other unanticipated problems involving risks to study subjects.

This letter is your Continual Review Approval Letter and also the 30 Day Administrative Extension Notification. As you know, your initial approval from BioMed IRB for protocol 06012006 under Dr. Kevin Bickford was set to expire on June 07, 2011. Your Continual Review Report was received by the IRB on June 22, 2011 after the last available IRB meeting that your request for continuance could be reviewed.

An administrative extension for continual approval was granted to your site for the above referenced study and your application for continual review was approved by the IRB at the June 24, 2011 meeting.

Please note that the study is set to be reviewed annually and the cycle for review will not change due to the administrative extension. The review cycle will continue to occur on June 7th, as originally assessed by the IRB.

BioMed IRB is comprised of a diverse group of individuals in accordance with the Federal Regulations and the International Conference on Harmonization, Global Harmonization or other appropriate guidance for Good Clinical Practice. BioMed IRB follows written procedures for performing review, documenting meeting minutes, disclosure of member conflict of interest prior to deliberation or voting, as well as the retention of all records containing research materials as required by the Code of Federal Regulations (21CFR parts 50 and 56; and 45 CFR part 46).

On behalf of the BioMed IRB, I certify that the information contained in this letter is true and correct as verified by the minutes and records of the BioMed IRB.

Please keep a copy of the continual review material, as well as a copy of this letter, in your files for future reference. Should you have questions or concerns, please do not hesitate to contact this office.

Sincerely,

Authorized Signature

Study Manager
Title

Amelia Cline
Printed Name

June 24, 2011
Date

Annex 2

Title: Clinical Research Sample Collection
Protocol ID: Protocol # SLR 0311 T4/TSH Project / 03/30/2011
Release Date: 03/30/2011
Sponsored By: SLR Research

1. Study Purpose

This protocol has been developed in association with research divisions of several major diagnostic companies. The purpose of this study is to obtain human biological material from multiple physicians groups located on the mid-East coast of the USA. The biological samples will be used in the development and improvement of diagnostic test kits and devices. Diagnostic assay development requires collection of human biological samples from a wide range of participants to evaluate the specificity and sensitivity of the assay. For the purpose of this study, "Participants" shall be defined as any individuals currently living in the USA and being evaluated for a thyroid disorder and classified into one of the following groups: Hyperthyroid and Euthyroid; donors who have been evaluated by the participating physicians deemed physically able to participate, and are over 18 years of age.

2. Confidentiality

The participant's identity will be strictly protected. Pre assigned numbers will be used for all samples, and will be used for identification in all reports and communications relating to their participation in the study information from this study will be used by SLR Research Corporation and it's associates, and may be submitted to the FDA, or other regulatory bodies including the IRB. The participant's privacy will be protected to the extent permitted by the applicable laws and regulations; however, absolute confidentiality cannot be guaranteed. The study will be compliant with all current HIPAA regulations.

3. Study Site Selection and Personnel

A number of sites have been selected and up to 1,200 participants will be enrolled. The number of enrollees may be increased as needed. Each patient may participate only once. The Site will be required to have adequate staff to assure the accuracy and compliance with study procedures.

4. Study Population

The patient population for this study will consist exclusively of individuals who are patients of our approved study sites located on the mid-East Coast of the USA.

5. Subject Inclusion / Exclusion

5.1 Inclusion Criteria

All patients of the study sites who are at least 18 years of age will be eligible to enter the study. Specific populations of individuals currently being evaluated for a thyroid disorder and classified into one of the following groups: Hyperthyroid and Euthyroid.

5.2 Exclusion Criteria

- Those individuals previously enrolled into this clinical study.
- Individuals diagnosed with a severe non-thyroidal illness. This is defined as a state of dysregulation where levels of T3, T4, FT3 and/or FT4 are abnormal although the Thyroid gland does not appear to be dysfunctional. In practice, NTI is reported to be usually associated with critical illness or starvation. Examples: chronic renal failure, liver cirrhosis, advanced (active) malignancy, sepsis, trauma, prolonged fasting or starvation, heart failure, MI, and any psychiatric disorder.
- Those patients not meeting the established inclusion criteria.
- In addition, patients who have been deemed not physically able, or whose conditions may be negatively affected by participation, will not be allowed to participate.

6. Study Procedures

- The PI (or designee) will explain to the patient that they may be asked to donate blood samples which may be used for viable medical research and diagnostic assay development. This process will take approximately 10 - 15 minutes. Blood volumes will not exceed 40 mLs.
- If the study participant agrees to participate and signs the Study Participant Consent, the PI will have permission to save any donor samples and complete the patient profile.
- The patient profile (also known as the Case Report Form "CRF") will be identified by a unique number that does not link the document to the patient in any way.
- A copy of the Study Informed Consent will be provided to the participant.
- The participant may elect to withdraw from the study at any time, or may be removed from the study by the PI at any time.

7. Adverse Events

In the event that there is a research related injury to the participant, the sponsor shall only be liable for medical expenses that specifically relate to the incident which are not covered by the participant's insurance plan. Sponsor is not liable for lost wages, other losses, or long term disability which results from such incident.

8. Specimen Inclusion/Exclusion Criteria

The following Inclusion and Exclusion Criteria are to be used as guidelines for the selection of specimens who fit the criteria for this Study:

8.1 Inclusion Criteria

- Minimum volume requirement of 15 mL of serum per donor.
- Storage: Liquid at all times.
- All locations will utilize the same collection tubes and follow standard procedures dictated by tube manufacturer with regards to clotting and centrifugation times.
- Specimen results will be evenly distributed within the following groups:

GROUP A: Hyperthyroid (N = 30)

- A1: 10 patients with suppressed TSH, around 0.01 mIU/L
- A2: 10 patients with TSH values between 0.01 – 0.1 mIU/L
- A3: 10 patients with TSH values between 0.1 – 0.3 mIU/L(Ortho Vitros) or TSH values between 0.1 – 0.35 mIU/L (Siemens)

GROUP B: Euthyroid (N = 30)

- Patients with TSH values between 0.3 – 3.0 mIU/L (Ortho Vitros) or TSH values between 0.35 – 4.5 mIU/L (Siemens)

GROUP C: Hypothyroid (N = 40)

- C1: 20 patients with TSH values between 3.0 – 50 mIU/L (Ortho Vitros) or TSH values between 4.5 – 50 mIU/L (Siemens)
- C2: 20 patients with TSH values > 50 mIU/L up to 100 mIU/L. Even distribution (if possible).

GROUP D: Hyperthyroid (N = 30)

- D1: 15 patients with FT4 values > 2.2 ng/dL (Ortho Vitros) up to 3.1 ng/dL. Even distribution (if possible).
- D2: 15 patients with FT4 values > 1.8 ng/dL (Siemens) up to 3.1 ng/dL. Even distribution (if possible).

GROUP E: Euthyroid (N = 30)
Patients with FT4 values between 0.78 – 2.2 ng/dL (Ortho Vitros) or FT4 values between 0.8 – 1.8 ng/dL (Siemens). Even distribution.

GROUP F: Hypothyroid (N = 30)

- Patients with FT4 values between 0.23 -0.78 ng/dL (Orth Vitros) or FT4 values between 0.23 ng/dL – 0.8 ng/dL (Siemens). Even distribution.

8.2 Exclusion Criteria

- Collection in an incorrect container
- Hemolyzed specimens
- Specimens that do not meet Inclusion criteria
- Specimens that have been frozen

9. Specimen Collection, Processing and Storage Requirements

- Serum
- Refrigerate samples until ship date.
- The samples are to be shipped directly to SLR Research Corporation unless other arrangements are made by the sponsor.
- Specimens will be stored refrigerated prior to processing.
- Each 15 mL donor sample will be aliquoted by 0.5 mL increments into KTS labeled Sorenson Bioscience 2 mL skirted vials and sealed with paired O-ring cap.
- Specimens will then be assembled into "panels" within 50 place racks.
- After assembly, specimens will be frozen at -70C or below until time to ship.

10. Study Monitoring

A representative of SLR Research Corporation will conduct an audit of the site at least once per year to insure that all of the protocol requirements are being followed. In addition, individuals from BioMed IRB and the FDA are entitled to do the same, provided that the audit is confined to documents, employees, and areas of the facility specifically related to the study.

11. Study Materials

SLR Research Corporation representative will provide the Principal Investigator with individual packets of the Study Subject Informed Consent, Patient Profile, etc. The Principal Investigator will retain completed copies of patient consent forms and case report forms for a period of 3 years after the termination of the study. In the event of an audit, documents shall be made available for review by the Sponsor or by the FDA with reasonable prior notification.

12. Processing Patient Profiles

- Check that the unique patient numbers on the specimen tubes match the subject ID numbers on the patient profile. This number will be solely used to link the patient profile and sample. The patient identity will remain confidential with the Principal Investigator and SLR Research Corporation.
- Patient profiles will be forwarded to SLR Research Corporation on a regular basis as agreed upon.
- Fully complete the patient profile. Provide as much detail as possible.

13. Contact Information

Contact SLR Research Corporation with any questions related to the Research Study:

Sponsor Contacts:
Jessica Bickford, Vice President
SLR Research Corporation
PO Box 2729
Carlsbad, CA 92018
760-930-9496 / Fax 760-930-9158

14. Regulatory Obligations

The Clinical Study documents and Protocols are regulated under guidelines mandated by the FDA, local regulations and country laws.

Central IRB oversight is maintained by BioMed IRB, San Diego, CA.

SLR RESEARCH	CONTROLLED LOG		
DOCUMENT NUMBER FM-38	REVISION 1	EFFECTIVE DATE 30MAR11	PAGE 1 OF 1
DOCUMENT TITLE **Ghent Process Log**			
DOCUMENT INITIATOR CHRISTOPHER ROUTH	DATE 30MAR11	APPROVED BY JESSICA BICKFORD	DATE 30Mar11

Donor Lot: _____ Date Received: _____

Upon receipt samples are stored in walk in refrigerators.

**** Upon assembly samples are stored in -80 freezers.***

Assembly Start Time	Verified By:	Assembly Finish Time	Verified By:
Time placed in -80	Verified By:		

Sample of the CRF data sheet to receive for each patient

SUBJECT INFORMATION (GENERAL):

DOB:6/14/70	Gender:M	Race:B
Smoker:No (PACKS PER WEEK)	Alcohol:No (DRINKS PER WEEK)	
Weight:219	Height:71"	

DIAGNOSES:
Stage IV / Colon CA

SURGERIES:
Colectomy

MEDICATIONS:
Compazme
Veloda
Pepcid